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THE S I S

For the Degree of M.D., Edinburgh University,

THE AETIOLOGY of PAGET'S DISEASE of BONE
With Special Reference to its Relation to Neoplasia.

BY

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SPECIAL REFERENCE to its RELATION to NEOPLASIA..

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for providing the numerous books consulted in this
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I. P R E F A C E .

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ON the AETIOLOGY of PAGET'S DISEASE of BONE with
SPECIAL REFERENCE to its RELATION to NEOPLASIA.

During the past winter I have had the good fortune to observe a case of Paget's Disease of bone, in which there occurred in the diseased bones multiple sarcomatous developments. Owing to the amputation of one of the affected limbs, I was given the unique opportunity of studying the minute pathological changes in the bones and at the same time of watching the course of the disease clinically.

The combined result of these pathological and clinical studies was to disclose certain data, which form the foundation for this thesis.

Sir James Paget first drew attention to the frequency of neoplasia in the later stages of the disease. In a résumé of his study of 23 cases, 20 years after he first described the condition, he declared that in his experience " the frequency of cancer or sarcoma occurring in those affected with the disease is confirmed." Of the 23 cases only eight have been traced to the end, and of these five died of malignant disease.

This/

This fact, confirmed as I believe it is by the observations of others, is decisive as to the intimate relation between osteitis deformans and the formation of malignant tumours. I do not venture to guess what the relation is. It is as if by some gradual general change the osteitis made a patient very liable to cancer or sarcoma, for it has in every case existed many years before the malignant growth appeared, and the liability is general rather than local for the morbid growths do not form exclusively or even chiefly in the diseased bone. But at present I think we had better be contented with the fact and wait for the explanation till a much larger number of cases have been examined after death. It will be useful to find whether the relation of osteitis be to morbid growths in general, not only to malignant. Among the 23 cases I have collected one had many subcutaneous fatty tumours another had many simple molluscous outgrowths."

It is this statement of Paget that we would make our main thesis. This tendency towards neoplasia has been a striking feature in the case studied by me. It has led to a careful investigation of the literature in order to determine the extent/

extent to which later case reports have confirmed Paget's observations, to determine how far the neoplasms recorded have originated in the disordered bone, how far they have been heterotopic, to discuss the association between disturbed function of a tissue and the eventual appearance in the same of aberrant cell growth, and doing this to recognize as sharply distinguished two orders of neoplasia, the one originating as strictly localized well defined cell republics, the other as a generalized and diffuse modification of growth and function of particular elements of a tissue. While lastly the frequency with which, as Paget pointed out, this bone disease has associated with it the development of neoplastic states at a distance has led us to discuss whether there must not here be some common cause in action, and to fall back upon some view of metabolism, or disturbance in the internal secretions, as underlying both the development of Paget's disease and the liability to aberrant tissue growth and neoplasia of other orders. For as regards the ordinary and extraordinary growth of various tissues the investigations of recent years have more and more impressed upon us the controlling influence of those/

those glands which afford an internal secretion. And thus recognizing some relationship between Paget's disease and these anomalies of cell growth we have been led towards that theory which ascribes the disease in question to some fundamental disturbance in the internal secretory activities of the organism.

PAGET'S/

II.

PAGET'S DISEASE OF BONE.

Historical sketch and description of signs and symptoms. Differential diagnosis, prognosis, treatment, etc.

At a meeting of the Royal Medical and Chirurgical Society of London in 1876 Sir James Paget described some of the results of a "study he had made of a rare disease of bones."

He gave an account of five cases which he had seen in practice, the disease being characterised by the following features: -

"It begins in middle age or later, is very slow in progress, may continue for many years without influence on the general health, and may give no other trouble than those which are due to the changes of shape, size and direction of the diseased bones. Even when the skull is hugely thickened, and all its bones exceedingly altered in structure, the mind remains unaffected.

The disease affects most frequently the long bones of the lower extremities and the skull, and is usually symmetrical.

The bones enlarge and soften, and those bearing weight yield and become unnaturally curved and misshapen. The spine whether by yielding to the weight of the overgrown skull, or by change in its own structures, may sink and seem to shorten, with/

with greatly increased dorsal and lumbar curves; the pelvis may become wide; the necks of the femora may become nearly horizontal, but the limbs, however misshapen remain strong, fit to support the trunk.

In its earlier periods, and sometimes through all its course, the disease is attended with pains in the affected bones, pains widely various in severity and variously described as rheumatic, gouty or neuralgic, not especially nocturnal or periodical.

It is not attended with fever. No characteristic conditions of urine or faeces have been found in it. It is not associated with syphilis, or any other known constitutional disease, unless it be cancer. It deserves note that in 1876 the term "cancer" was commonly employed to denote any malignant growth whether carcinomatous or sarcomatous. In three out of the five well marked cases that I have seen cancer appeared late in life; a remarkable proportion, possibly not more than might have occurred in accidental coincidences, yet suggesting careful inquiry.

Mr. Butlin describing the pathological appearances and histology of Paget's cases found the leading/

leading characteristics were as follows: -

The periosteum was not visibly changed nor adherent. The outer surface of the walls of the bones was irregularly and finely nodular, deeply grooved with channels for the periosteal blood vessels, and finely but visibly perforated in every part for transmission of small vessels. The outer compact bone seemed increased. The greater part of the walls of the bone was altered into a hard porous, finely reticular substance, like very fine coral. In some places were small ill defined patches of pale, dense and hard bone, as solid as brick. In the compact covering of the articular ends of the long bones and of the patellae and neck of the femur the increase in thickness was due to the encroachment on the cancellous texture by newly formed bone.

SKULL: The bone was softened and could be cut fairly easily: it was four times its normal thickness: the outer surface was finely porous, the inner surface showed deepening of the grooves for blood vessels. The distinction between the diploe and the outer and inner tables was lost to a large extent, the bone being made up of porous cancellous bone with the spaces filled with soft reddish substance, a kind of medulla.

MICROSCOPICALLY:

MICROSCOPICALLY: The number of Haversian systems and canals were much diminished. The Haversian canals were enormously widened, many of them confluent, and thus the appearance of a number of communicating medullary spaces was obtained, an appearance which was rendered still more striking by the presence in the canals of a large quantity of ill developed tissue in addition to the blood vessels. With a high power the contents of the Haversian canals were seen to consist generally of a homogeneous or granular basis containing cells of round or oval form. Myeloid cells were not numerous. Fibres and fibro-cells were present in large quantities.

The walls of some canals were lined by a single layer of osteoblasts. The presence of the new bone was most evident in the periosteum of the tibia, it was softer and less developed than the bone from which it sprung.

Paget was the first to describe the disease as a definite clinical entity, but the symptoms had already previously been noted by other observers:-

Sancerotte (Melanges de Chir, Paris, 1801), describes the case of a patient who died, aged forty, and in whom all the bones had begun to enlarge seven years/

years before death, associated with rheumatic pains.

Rullier (Bulletin de L'Ecole de Med. Paris, 1912) tells of a man who died in Hospital with general increase in the size of the skull, clavicles, pelvis and ribs. Wrany, (Prager Vierteljahrschrift, 1857), described a case of spongy hyperostosis of the skull, pelvis and femora vertebrae, kyphosis.

Jonathan Hutchinson tells of a parietal bone which he saw in the Royal College of Surgeons' Museum which had been found in an Egyptian royal tomb, (5500 years old), and which was a typical example of Paget's disease and probably the most ancient case on record. Czerny, in 1873, had described under the name of a "Lokale Malacce des Unterschenkels" a case which evidently was one of Paget's disease.

Shortly after Paget's communication, cases were reported by Bryant, Cayley, Howse, Goodhart, Lunn, Morris, Symmond, Treves, Barlow, Boulby, Pick, ~~and~~ ^{etc.} In the French papers also reference was made to the disease.

Paget suggested the name of "Osteitis Deformans", as he regarded the condition as a chronic inflammatory one. In 1882, Paget reported seven new cases, and in 1892, he had collected twenty-three. In 1890 Thebierge reported forty-four cases: Jonchonchy 1893, counted sixty, forty occurring in England and/

and twenty in France.

At first few cases were recorded out of England, but of recent years the proportion of cases abroad has advanced (as knowledge of the disease has spread), and now cases have been reported from all the countries of Europe and also in North and South America.

Paget's disease of bone is not confined only to the human subject.

Eminent French authorities such as Barthélemy and Dor have described an analagous condition occurring in horses in their interesting treatises entitled respectively:- "Maladie osseuse de Paget chez l'homme et maladie du son chez le cheval. Analogie de ces deux maladies". (Lyons 1901), and "De l'existence chez le cheval d'une maladie osseuse analogue à la maladie de Paget". (Revue de Chir. 1902.10th April.)

Goldmann also drew attention to a similar disease affecting the long bones which he demonstrated in the skeleton of a cock, one of the specimens in the Museum of the Royal College of Surgeons, London. (Munch.Med.Wochensch.1902.)

SIGNS/

SIGNS and SYMPTOMS.

The disease occurs chiefly in elderly men, the onset is insidious, often associated with rheumatic pains. Joncherie has described two varieties, painless and painful: it may for long remain localised to one bone or one limb, or, on the other hand, may rapidly become generalised. The tibia is the favourite site, after that the skull, clavicles, femora, other long bones, ribs, pelvis and vertebrae. The face bones and those of hands and feet remain usually free from disease.

The bones have characteristic deformities: they are thickened and the femora and tibiae tend to curve outwards and forwards. The natural curves of the clavicles are exaggerated, the upper part of the thorax is flattened: the lower part is relatively increased in size, the costal margin being everted and thickened. The head ^{is} thrust forwards. There is a wide dorso-cervical kyphosis, and the patient has a characteristically dragging gait. The shortened trunk and bent legs make the arms seem unduly long, and the attitude resembles greatly that of an anthropoid ape. Owing to the diminished expansion of the chest from the deformity, emphysema tends to occur. Arteriosclerosis is of frequent occurrence: also varicose/

varicose conditions of the legs, with eczema and ulceration and pigmentation of the skin are common.

Some cases have had scleroderma.

The nervous system is singularly free from disturbances as a rule, though cases have been reported of hemiplegia, paraplegia, chorea, bulbar paralysis, senile dementia, associated with Paget's disease. Eye changes are occasionally noted, such as retinal haemorrhages and choroiditis, and in ~~per cent of~~ ^{Some} cases glaucoma. Deafness occurred in 8.2 per cent of cases. In two there was loss of sense of smell.

Apart from those secondary to tumours, fractures are said to be very rare in Paget's disease, the softened bones tending rather to bend than break. ~~They occurred spontaneously after the onset of the disease in~~ ~~per cent of cases.~~ Union is usually good, (in contrast to what is noted in osteomalacea). The disease is protracted and lasts for many years - from one to forty. Death usually occurs from some intercurrent affection, unless malignant disease supervenes. Out of the reported deaths in one hundred and seventy cases recorded, 17% were associated with neoplasms.

The/

The general health in Paget's disease may be maintained for long: the rapid development of cachexia towards the end is usually the result of sarcomatous change. The blood condition has been examined in 10.4 per cent of the cases and was found to be normal, or to show a moderate secondary anaemia. The urine is normal, and there is no associated fever. Arthritic changes have occurred in ten per cent of the cases. The digestive system is not affected.

Sonnenberg was one of the first to draw attention to the importance of examining by means of the X-rays all doubtful cases of bone disease. His observations have been fully confirmed.

Radioscopic examination has materially aided the diagnosis of Paget's disease. The loss of the ordinary contrast between the compact and medullary bone and the alternation in size, irregularity or obliteration of the medullary canal, and the blurred alternations of light and shade (the result of the combined rarefaction and formation of new bone) give a picture which is characteristic and diagnostic.

In the case about to be described, numerous X-rays were taken, ^{see fig.} ~~and are included in the appendix~~ (among other features they show characteristically the rapidity of growth of the associated neoplasms/

neoplasms.)

The appearances of Paget's disease may be contrasted with the dense scleroses of bone, (1) in hereditary syphilis, (the deformity of the tibia in which disease, has a superficial resemblance to that of Paget's disease of bone), (2) in typical cases of osteomalacia also, the widely dilated medullary canal containing cysts gives a different picture.

DIFFERENTIAL DIAGNOSIS.

FROM RACHITIS: the distinguishing features are that in rachitis the condition is one of imperfect development of bone, whereas Paget's disease occurs in adult patients and in bone which previously seemed normal. The age of the patient and the X-ray appearance make the differential diagnosis a simple one.

FROM ACROMEGALY: in which the hands and feet and lower jaw are characteristically involved, (These bones are free from disease in Paget's disease).

Pierre Marie has called attention to the fact that in Paget's disease the head is triangular in/

in shape, with the base upwards, whereas in acromegaly the base of the triangle is downwards.

Most writers give a clear differential diagnosis between Paget's disease and osteomalacia: In well marked cases this is easy clinically; as we shall see later, however, the pathological changes in the two diseases are closely related. The angular curvature of the bone, the tendency to fracture, the characteristic deformity of the pelvis, and the age of the patient in a typical case of osteomalacia form a striking contrast to the typical picture of Paget's disease.

Hyperostosis of the Skull: in many cases this is probably merely a localised or an early stage of Paget's disease of bone. Prince describes a case which was first diagnosed as a case of hyperostosis cranii in contra-distinction to Paget's disease, but which later developed typical deformities of the long bones.

PROGNOSIS. The course in Paget's disease is chronic and progressive: life may not necessarily be shortened by the disease: in a fairly large percentage of cases death results from malignant disease with cachexia. The frequently associated arteriosclerosis tends to make the prognosis as regards life graver.

TREATMENT/

TREATMENT.

No treatment has proved to be of any service. The iodides and mercury have no effect in arresting the progress of the disease. Thyroid extract, adrenalin, pituitary extract, and oophorectomy have all been tried without success. In some cases amputation of a limb has been undertaken for relief of pain, (Schmeiden, Gaucero and Clutton).

ANALYSIS & DISCUSSION of OTHER THEORIES & CASES.

ETIOLOGY.

/

Clinically, Paget's disease of bone is easy of diagnosis; its leading signs and symptoms are both striking and characteristic, it is only in the early stages that there can be any difficulty in recognising the condition. The etiology, however, is found to be as obscure as the diagnosis is clear, and the overwhelming number of conflicting theories propounded by writers on the subject is an index to our ignorance on this point. Many theories have been advanced and enthusiastically upheld by their/

their advocates, yet the evidence in support of any of these on investigation proves to be slight and inconclusive. In order to weigh and investigate these theories, we have made an analysis of 170 recorded cases of Paget's disease; the original reports have been consulted where these were available, and the results tabulated, so that the reader can himself weigh the evidence in favour of any particular theory, (for tabulated analysis of cases see appendix.)

The various theories advanced and the arguments in their favour may now be discussed.

HEREDITY.

From a study of twenty-three cases, Paget failed to find any tendency for the disease to run in families. The cases are so relatively infrequent that it is difficult to dogmatise on this point, but Berger, Chauffard, Lunn, Pic, Kilner, White, Kippel and Pierre Wiel, Robinson, Walter, Oettlinger and Agasse Lepont have reported cases occurring either in two successive generations or in two members of the same family. Oettlinger describes a father and two sons, all marked examples of this disease.

GOUT AND RHEUMATISM: The fact that for the first few years after Paget described the disease almost all the reported cases occurred in England gave the impression that environment is a factor and the frequency of gout and rheumatism in England gave color to the view that they were intimately associated with the disease. Many patients, however, have no gouty or rheumatic history and the reason for this apparent frequency was probably that an Englishman had discovered the disease and therefore the knowledge of it was brought before the profession more forcibly in Great Britain than abroad, for later on the percentage of cases reported on the Continent and in America rapidly increased. Langer-eaux in his paper 'l'Herpétisme' strongly advocated the theory of its rheumatic origin. There is no doubt that many cases have a history pointing to this and in many there is an associated rheumatoid arthritis; but it must be taken into consideration that the age at which Paget's disease occurs is one characterised by a tendency to rheumatic affections, and when the great frequency of rheumatism is taken into account and the equally great rarity of Paget's disease, the view that the association of the two diseases is a coincidence is the more probable. This will be referred to later.

TRAUMA: /

TRAUMA: A percentage 11.5% of cases have a history of severe trauma before the onset of the disease. While this may have some determining influence in the causation too much stress cannot be laid on it when we remember how apt patients are to seek for some explanation of any illness, and to attach great importance to trivial accidents which probably had nothing to do with the disease in question. Von Recklinghausen was one of the advocates of the theory of the mechanical causation, pointing out that the bones most frequently diseased were those most liable to injury and strains.

ARTERIOSCLEROSIS: Over 50% of the cases have cardio-vascular changes and at first sight this seems to indicate some intimate connection between the two diseases. The frequency of arteriosclerosis at the age at which Paget's disease usually manifests itself, is probably the explanation of this striking coincidence. Many marked cases of Paget's diseases, among others our own case, have no trace of cardio-vascular disease. Some French writers, however, have attributed the pathological changes in the bones to arteriosclerotic changes in the nutrient vessels. This theory, however, does not seem adequate. Beclere and Gaillard tried to prove that/

that localised arteriosclerosis might be responsible for the cases in which only a few bones are affected; Menetrier and Gauckler have shown the analogy which exists between lesions of Paget's disease and those of visceral sclerosis. Klippel, however, points out that this does not explain the cases in which Paget's disease starts in early life, also the cases in which the disease seems to follow on traumatism.

CHRONIC INTOXICATION BY MINERAL ACIDS.

Oettlinger and Agasse-Lapont in the three cases occurring in one family reported by them, noticed the fact that all their cases were laundry workers, and having in the literature found 13 of 20 cases had occurred in people exposed in their occupation to intoxication from mineral acids, (printers, plumbers, laundry workers, steel workers, etc. etc.) sought some explanation of the disease in an intoxication due to chemicals used in their work. The survey of cases of the disease occurring in patients of all classes and occupations makes one dismiss this theory again as an interesting coincidence but nothing more.

The theories which are most commonly held
at/

at the present time are, (1) Congenital syphilis, (2) Trophoneurosis, (3) Disturbance of internal secretion. I. The view that Paget's disease is a late manifestation of congenital syphilis was first advanced by Lannelongue and was enthusiastically taken up by the French school. In a paper entitled "Notes sur la Syphilis osseuse Hereditaire chez les nouveaux nes (Maladie de Parrot), chez les enfants et les adolescents, chez les adultes et les vieillards (maladie de Paget), read before the Academy of Paris, 1903, Lannelongue stated that undoubtedly Paget's disease was merely a late manifestation of hereditary syphilis, and, in support of this argument, declared that this was possible even in patients showing no Syphilitic stigmata and healthy until late adult life; but added that these stigmata were probably not found in recorded cases because they were not looked for. Lannelongue also drew attention to the fact that the new formation of bone took place not on the concavity of but on the convexity of the diseased bone; thus destroying the argument of those who attributed the formation of new bone to a compensatory protective process. Fournier in the main agreed with Lannelongue although he admitted that some cases of Paget's disease/

disease might be para-syphilitic. Other French doctors, such as Vincent, wrote strongly in favour of the syphilitic theory and described cases cured by anti-syphilitic treatment.

Authorities like Jonathan Hutchinson, Thibierge, Pierre Marie, on the other hand, have declared that there is no connection between the two diseases and Weber emphasized especially the age of development of first symptom, the character of the pain, which did not yield to treatment, the distribution of the affected bones, the absence of bossing, the tendency for malignant tumours to supervene, as being distinguishing features in the differential diagnosis between the two diseases, which, though they might coexist in the same patient, have no relationship to one another.

Our analysis of the cases shows (1) A striking absence of history or signs of syphilis, congenital or acquired. They are present in but 4 per cent of the cases. (2) The negative results of anti-syphilitic treatment (in some cases this seemed to do harm) which had no influence on the progress of the disease though occasionally it eased pain. (3) The only cases "cured" by anti-syphilitic treatment were from the reports most probably not cases of Paget's disease at all but of syphilitic disease of bone.

The/

The Wassermann reaction has, however, conclusively decided this point, as in all the recorded cases in which it has been tried it has been definitely negative.

TROPHO-NEUROSIS: The theory that Paget's disease is a trophoneurosis has been advanced by many observers who have seen in it a condition analogous to Charcot's disease. Gilles de la Tourette from a study of two cases with autopsy, concluded that the bony alterations were the result of trophic changes involving the bulb and grey matter. In one of his cases he found an oedema of the cerebrum and cord, and pale yellow discoloration of the posterior columns:- not a true sclerosis but still resembling somewhat the changes seen in other diseases of the spinal cord, e.g. Tabes. In his second case he describes paleness of the columns of Flechsig, especially in the middle and inferior dorsal regions, which he attributed to rarification of nerve fibres. The evidence is not however very convincing as the changes were indefinite enough to support the view that they may have occurred post mortem, and especially when the writer admitted that there were no nervous symptoms during life. Pierres and Vaillard, (Archives de Physiol. Normal. & Path., 1885), attributed the disease to degeneration/

degeneration of the nerves entering into the nutrient foramen of the bone; Hudelo and Heitz, and Levi found neuritic lesions. They remark that in three cases in which the nerves have been examined post mortem they were found diseased, but probably these lesions are merely due to degeneration of the arteries and atheroma of the vasa vasorum.

Indeed one of the striking features of Paget's disease is the absence of nervous disturbance even in very marked cases and in late stages. The small percentage of associated nerve symptoms that do occur would seem rather to be due to the accompanying arteriosclerosis than to primary disease of the nervous system.

The small number of autopsies and their incomplete nature do not tend to help us on this point. Stilling and von Recklinghausen found a small cervical glioma in one of their cases. Mackay had Huntington's chorea associated with his case. Bulbar paralysis was described in another, but these are such varied conditions that one feels that they more accidental than anything else. Against the argument in favour of Paget's disease being a dystrophy may be cited (1) the previous good general health of the patient (2) the absence of symptoms of nervous disease, (3) the advanced age/

age at which the disease manifests itself and, (4) the absence of any definite distribution in the bones affected.

DISTURBANCE OF INTERNAL SECRETION: Recently the theory that Paget's disease is the result of disturbance of some internal secretion has been advanced and has been taken up with increasing favour.

Metabolism experiments have been made in some cases and the results are interesting as showing an increased excretion of calcium and phosphorus and a slight retention of magnesium (McCrudden, Bruere). Askanazy has drawn attention to the fact that in one case the thyroid gland was enlarged, and more recently McCrudden, Mainwaring, White, Higbie and Elles, have reported cases which they attribute to metabolic disturbances. Taylor was one of the first to suggest that it was caused by some anomaly of nutrition.

Many other observers have attributed the disease to some abnormality of internal secretion and have tried various extracts of the glands in question as therapeutic agents. Byron Bramwell gave adrenalin to his patient, White gave thyroid extract. Hochheimer/

Hochheimer performed a double oophorectomy thinking a disordered ovarian secretion might be the cause of the condition. But the results of all such treatment have been negative as far as the arrest of the disease has been concerned, though some claim that the insomnia from which these patients suffered had been relieved to some extent by thyroid ^{extract} ~~Ext.~~ where all other drugs had failed.

The post mortem findings do not help us much in considering this question. In many reports no mention of the Ductless glands is made, in others the notes are too vague to be of much value.

While this theory has undoubtedly a bearing on the disease, it in itself is inadequate to explain the mode of occurrence.

III. HISTORY OF OUR OWN CASE.

The patient D.G.YOUNG, aet. 56, married. Admitted November 19th 1910, complaining of "Rheumatism in the bones and bandy legs". Born in Montreal - married 20 years. Wife and children alive and well - Wife had two miscarriages (first two pregnancies) - Occupation Jeweller.

No venereal disease. Always enjoyed good health. Moist eczema of legs for 15 years. Smokes to excess, also drinks. Appetite good.

F. H. Father dead, pneumonia. Mother dead, old age. No history of tuberculosis, rheumatism, or cancer, or of bone disease.

P. E. Four years previously, skin over the anterior part of the left "shin" became inflamed. Here was considerable pain in the bone, and some swelling, and patient was unable to go out for two weeks, when the symptoms gradually subsided. He did not feel ill enough to consult a doctor.

Since the patient has had "rheumatic" pain in both legs, more or less constantly, worse at night, but never bad enough to make him cease work. At times these pains are "cramplike" in the calves of the/

the legs, causing the "muscles to be drawn up in bunches".

Soon after the onset of these pains his legs began to bend, and this deformity has steadily advanced. The bending has been more noticeable during the past year, and his friends have frequently referred to his bandy legs and altered gait.

His height has gradually diminished, and he states he has lost almost 4" in height. There has also been a gradual increase in the size of his head, and he now has to wear hats two sizes larger than he did two years ago.

About two months before admission, patient began to have dull, aching pain in the muscles and bones of the right forearm. He was obliged after a few days to give up work on account of the severe pain and tenderness of the arm. He consulted a doctor, who told him he had muscular rheumatism. A few days later the pain extended to the right shoulder joint and the muscles around it.

The pain still continues, but is less severe, and no longer constant. Patient is unable, however, to use the arm, and indeed cannot lift it without pain in the shoulder joint. He prefers to keep it fixed/

fixed at a right angle.

Since the onset of pain in the forearm his radius has been rapidly bowing. Throughout his general health is good, and he has lost little weight. No mental symptoms.

The patient is a man of small stature. Hair moderately gray, brow rather prominent, no exostoses. Eyes react to light and accommodation movements normal. Tongue large, rather pale. Throat healthy. No glandular enlargement.

THORAX.

Right shoulder is unusually prominent, movement impaired, and there is loss of the bony points. The head of the humerus seems enlarged, the bony points on the right scapula are ill-defined, though the scapulae appear equal behind.

The right clavicle is bowed forwards, and appears more circular than the left. The chest is flattened, with broadening about the lower costal margin. Expansion fair and equal. Breath sounds normal.

Heart. Apex beats = 4th interspace 8.5 c.m. from under sternum.

Cardiac dulness. Upper border = 3rd rib.

Right border = Right lateral
sternal line.

Left/

THORAX. Left border = 8.5 c.m. from middle sternum.

Auscultation. Heart sounds regular and closed in all areas.

Pulse. 78 per minute, regular in force, time and volume.

Artery faintly palpable. Pulse strong. Blood Pressure 112 mil.Hg. (Riva Rocci).

BACK. Old scar on back of neck. No change visible in spine. No tenderness.

Auscultation. Natural breath sounds.

ABDOMEN. Rather flat. Outlines natural.

Caecum felt in right iliac fossa.

Spleen and liver not palpable.

OSSEOUS SYSTEM.

SKULL. There is slight general enlargement of the cranial vault, but no asymmetry or exostosis (see X ray photograph taken on November 25th 1910, which shows also the thickening of the cranial bones.)

SPINE. General wide kyphosis, but no tenderness nor rigidity of the spine.

THORAX./

THORAX. There is some rigidity of the upper half of the chest, with diminished expansion, the lower part of the chest is unduly prominent, and the costal margin is abnormally near to the iliac crests. Owing to this deformity, the breathing is chiefly abdominal.

CLAVICLES. As already stated, there is an increase of the natural curves of the clavicles and some thickening of these bones; this is more marked on the right side.

UPPER EXTREMITIES. For condition of right shoulder see previous note. (See also X ray photo.) The right humerus is considerably thickened and curved anteriorly. The X ray photograph shows irregularity and narrowing of the medullary canal, and areas of irregular condensation and rarefaction.

BONES OF FOREARM. Left forearm is normal. Right forearm shows marked bowing of the radius, and on palpation this bone is found to be thickened, especially in its lower two thirds. X ray photograph of November 25th, 1910 shows general thickening, with areas of condensation and rarefaction. There is slight general thickening of the right ulna.

LOWER LIMBS. The femora show general thickening/

thickening and anterior curving. The X ray photographs (Vol. 116) show the above, and also the irregular areas of condensation and rarefaction. There is some thickening of the internal condyles, more especially the right.

TIBIAE Right shows marked antero-external curving and great thickening of the bones. The X ray photograph (Vol. 117) of the right tibia shows beautifully the typical appearances of an advanced case of Paget's disease, namely the loss of the medullary canal, the great thickening of the bone and the areas of condensation and rarefaction. The left Tibia, on the other hand, shows the thickening, but not the condensation and rarefaction, it being in an earlier stage of the disease.

The fibulae show the same changes, but to a less extent.

The bones of the hands and feet show no abnormality.

HAEMOPOITIC SYSTEM.

The thyroid gland is not palpable. Spleen not palpable. No lymphatic glandular enlargement.

BLOOD. Repeated examination showed a progressive/

progressive secondary anaemia.

Red Blood Corpuscles. 2,900,000.

2,700,000.

2,500,000.

Hb. 65% .

60% .

60% .

Blood films show no poikilocytosis, no nucleated red blood corpuscles seen. No myelocytes. No eosinophilia. Leucocytosis varied from 7000 to 8000, except on an occasion in January, when it was 28,000, the patient at the time suffering from an acute double otitis media.

Temperature remained normal throughout illness, until the development of the bed-sores, after which it swung irregularly up to 100°.

WASSERMANN reaction definitely negative.

PROGRESS NOTES.

December 10th, 1910. Increased thickening and pain in right forearm. X ray photograph of right forearm shows a rarefaction in mid third of radius, suggestive of commencing tumour formation.

December 19th, 1910. The condition of the patient/

patient is distinctly worse. While still able to go about, he is distinctly weaker. The bowing of the right forearm is increasing, and an X ray photograph taken to-day shows what appears to be a localised new growth in the middle third of the radius (see X ray, No.) and compare with X ray No. taken three weeks previously).

January 7th, 1911. There is now an obvious tumour in the middle third of the right forearm. It is of somewhat gelatinous consistence, and a spontaneous fracture has occurred. (See X ray, No.).

January 9th. Exploratory incision made over tumour of radius, and a small portion removed for microscopic examination.

The patient began to emaciate and lose appetite and strength. The pains in the right forearm and shoulder became more intense, and his condition was further aggravated by a double acute suppurating otitis media, causing a rise of temperature to 100°.

The right shoulder and upper arm has become slightly oedematous, and the skin glazed and slightly reddened. The skin over the upper two-thirds of the humerus pits slightly on pressure. The right lung in axillary region gives prolonged inspiration, and/

and the sounds are much harsher than on the other side.

HEART. Mitral systolic murmur.

January 27th. Legs and abdomen. oedematous. X rays taken to-day. That of right humerus shows general increase in the size of the neoplasm in the head of the bone, and the presence of a spontaneous fracture just below the surgical neck. That of the right forearm shows the spontaneous fracture of the radius already referred to, and an increase in the size of the growth.

February 2nd. Radiograph shows fracture of Humerus 2" below head. Dr. Bell examined patient, decided that if the arm were removed it would ease the intense pain.

February 5th. Operation. Removal of right arm, scapula and outer half of clavicle.

The patient, although in a very weak condition beforehand, stood the operation well, and there was no shock.

February 8th. A small sessile swelling has appeared over the right frontal eminence, adherent to the bone and evidently in connection with it, about the size of a hazel nut, rather soft in consistence. Skin moves freely over it, and is unaltered in appearance.

February/

February 14th. Another small nodule has appeared on the skull, over left frontal eminence, the one on the right frontal eminence is gradually increasing in size.

Blood Count. Hb. 65. Red Blood Corpuscles, 2,900,000. Leucocytes, 8000.

Diff. Count. Pol.	75%.
Lymph.	10%.
Large mononu.	5%.

February 18th. Occasional twitching of the face reported by the nurses. Operation wound healing well.

February 25th. There is slight paralysis of the left side of the face and of the right leg. This came on gradually, without any subjective phenomena. The left eye cannot be shut, and patient cannot whistle. There is some drooping of the left angle of the mouth. The tongue, on being protruded, deviates slightly to the left. No sensory changes noted. Left eye, superficial corneal ulcer. Knee jerks, left brisk, right exaggerated. Ankle clonus marked on right side.

Right Babinski = +. There is slight exophthalmus of the right eye. The patient is losing weight rapidly and is in a state of great weakness and cachexia, he suffers from pains in the limbs and/

and resents being moved.

The deformities of the legs are rapidly becoming more marked. The femora are bent forwards and the internal condyles are especially prominent. The anteroexternal bowing of the tibiae is increasing. The pelvic crests seem thickened and everted. The lower costal margin is thickened and prominent, and the abdomen is crossed by two wide furrows. The patient is at times unconscious. He can take little nourishment, and the pain is severe enough to require opiates at night. There is oedema of both ankles, more especially of the right.

The distal end of the remaining portion of the right clavicle is gradually enlarging, the skin over it moves freely and the operation scar is healthy. Bed sores are developing over tuberculae. Urine contains no albumen or albuminose.

March 9th. Patient is now in a state of extreme weakness, and is unable to move in bed. There is loss of control of rectum and bladder, and bed-sores are developing over all points of pressure. In spite of preventive measures having been used, Three more small tumours have appeared on the skull, over the left parietal region.

Patient is still conscious and intelligent, but/

but suffers intense pain if moved and is rapidly emaciating. The right knee is swollen and painful, and there is a circular swelling one inch in diameter over the region of the external condyle of the femur. The internal condyle is greatly enlarged, and is the site of another tumour (about the size of a small tangerine orange), which is tender and rather soft in consistence.

At the upper end of the left tibia a small slightly elevated nodule has appeared, about the size of a shilling. Patient greatly resents having the limbs moved.

The exophthalmus of the right eye is increasing.

Fundi oculi examined by Dr Stirling and found normal. There is a left corneal ulcer (result of focal paralysis).

March 10th. No enlargement of spleen.

March 20th. Condition unchanged. The tumours of skull, clavicle, and femur are slowly increasing in size. Tumour right frontal region, Base diameter = $1\frac{3}{8}$ " elevation $\frac{1}{2}$ ". Other tumours on skull = $\frac{1}{2}$ " in diameter. They are also gelatinous in consistence and the skin is freely movable over them.

Blood Count. Red Blood Corpuscles, 2,500,000. Hb. 60%. Leucocytes 7,500. Blood film normal. No nucleated/

nucleated red cells or myelocytes.

Many bed-sores have appeared on trunk and limbs, and these show no signs of healing in spite of treatment. Progressive emaciation continues, but the patient seems comfortable and the mental condition is not affected. There is no defect of vision, no headache. He still received morphia for the pains at times and for his insomnia.

There is marked oedema of the ankles.

Normal Urine. No signs of metastasis in internal organs.

Metabolism experiments by Dr. Bruere showed a markedly increased calcium excretion, a slight increase of phosphorus excretion, with diminished magnesium excretion.

The patient died on April 18th. The official report has not yet been issued, but an interesting account of the autopsy was sent me and is appended.

There had been progressive growth of the tumour developing from the unremoved portion of the clavicle. The skull cap was intensely dense and ivory-like, with little signs of diploe, averaging one centimeter thick, and showing no definite tumour growths in association with the calvarium. The tumour of the scalp was not adherent to the bone, save/



save for a slight stalk about the thickness of a match stem, which stalk appeared to penetrate the bone and to be in continuity with a similar stalk of a leaf-like tumour, also unattached to the bone, spreading for several cc. between bone and dura.

The dura exhibited multiple miliary metastatic growths, apparently along the lines of the vessels, and this on both sides averaging about 3 mm. in diameter. Similar growths affected also the pia; the brain substance itself was uninvolved. There was further a tumour evidently extending along the auditory nerve and infiltrating the right petrous bone, cochlea, etc. This apparently explained the right-sided deafness. Another tumour of considerable size, evidently developing between the two layers of the dura in the anterior fossa had led to pressure on the right frontal region of the brain, on the one hand, (apparently explaining the progressive dulness and irritability of the patient), and, on the other hand, penetrated through the orbital roof, filling up the whole posterior portion of the right orbit, causing the eye to project. This tumour it was that presented itself above the right upper canthus. All these tumours were pale and sarcoma-like. There were no secondary growths in the brain substance proper.

The/

The extreme hardness of the skull cap prevented trephining to see the relationship between the scalp tumour and that on the inner aspect of the calvarium; as also it prevented a full study of the affected condition. There were no secondary growths recognizable elsewhere, save in connection with the thorax, to be presently noted. The ribs were free from new growth, as were the lower extremities. (? E.B.W.)

In the thorax were multiple small secondary growths scattered over both parietal pleurae. These were unconnected with the ribs. Similarly, there were abundant small secondary growths over the surface of both lungs. Between these was some inflammatory reaction and a small amount of exudate. There was one large mass of growth proceeding from the parietal pleura at the left apex. The lung substance showed in both organs multiple secondary growths, which stood out prominently against the rather shrunken lung substance. At the root of the heart there appeared to be an extension of the new growth over the pericardium on either side. The abdominal viscera were apparently all free from growth. The first rib was not involved in the growth from the clavicle, though this came to its surface.

Now I come to the point of greatest interest.

The/

The thyroid was extremely small and fibrous, in fact almost absent. The adrenals also were distinctly small; the pituitary smaller than normal; the pancreas relatively large and firm.

Lastly, on the left side there was a condition of interlobar empyema in pockets, and one of these small abscess cavities communicated with a bronchus.

PAGET'S DISEASE.

CASE of D. YOUNG.METABOLISM EXPERIMENT.

The experiment began with breakfast on Decr. 5th, 1910, and continued five days. The weight of the subject at the beginning was 81 lbs., and at the end 80 lbs.

During this experiment the subject voided 4560 c.c. of urine containing 46.11856 grammes of Nitrogen, and 80.66 grammes of feces (weighed after drying) containing 3.6 grammes of Nitrogen. The income of Nitrogen during the experiment was 38.97304 grammes. The average nitrogen balance per day was therefore :

Income in food 7.7946; outgo in urine and feces 9.9437; indicating a loss of 2.1491 grammes of N.

P₂O₅:-

	grammes		grammes
Total income	9.8578.	Total outgo	12.74335
Daily "	1.9715	Daily "	2.54867

Average daily loss 0.57717.

CaO:-

Total income	7.13027.	Total outgo	10.33625
" loss	3.20598.	Average daily	
		loss	0.64119

MgO:-

Total income	1.6192	Total outgo	2.19932
" loss	0.58012	Average daily	
		loss	0.116

(Signed) A.A. BRUÈRE.

IV. THE RELATION OF PAGET'S DISEASE OF BONE to NEOPLASIA.

As we have already indicated in the Introduction, Sir James Paget was decisive as to the close relationship existing between "Paget's Disease of Bone" and malignant new growths.

The earlier writers on Paget's Disease were much impressed by the frequency with which malignant disease was associated with Paget's Disease. Goodhart stated that in his experience half the cases of osteitis deformans suffered from malignant disease. Lunn and Thibierge report cases bearing on this point and Thibierge found, in a résumé of 18 cases reported by different authors, ten had died of malignant disease, and he declared that "Paget's Disease is progressive and is complicated almost constantly either by cardiac lesion or by malignant tumour". He at the same time stated that these malignant tumours were most frequently situated in the bones or in the organs in which metastases from malignant tumours of bones were usually found, and in the latter cases the autopsies had rarely been complete enough to be able to affirm that there was not a primary lesion in the bone. Howse also drew attention to the fact that the tumours were usually/

usually sarcomata and that many reported as "cancer" probably belonged to the former category.

Of recent years this view has entirely fallen into disfavour; writers on this subject either ignore the association of the two conditions or refer to them only to say that it is mere coincidence and natural, when one considers the age at which both malignant disease and Paget's Disease tend to occur. This attitude is the more regrettable from the fact that in autopsy reports the tumours, if they have occurred, are only casually referred to, and no accurate reports given of their structure, their relation to the surrounding bone, etc. Some of the tumours have not even been examined microscopically, so that one is left in doubt as to their real nature. Packard and Steele, in their excellent monograph on Paget's Disease, describing their own case where there was an associated sarcoma of bone, state, "the association with malignant disease, while present in our case, would seem to be not quite so frequent as is usually believed". The tumour in their case was giant-celled sarcoma, with metastases in pleura and brain; they do not, however, refer to the relation of the neoplasm to the surrounding bone, whether it was clearly defined, or as in our case, whether it imperceptibly merged into the surrounding tissue. Higbie and Ellis, in discussing/

discussing the etiology of Paget's Disease, referred to the coincidence in some cases of osteitis deformans and tumour growth as being interesting, they conclude however from a survey of the literature that "there is much less reason than formerly for believing there is a close relation, or indeed any relation, between the tissue changes in osteitis deformans and the growth of malignant tumours". Their reason for giving vent to this sweeping statement is because since 1902 they have in the literature only found mention of two cases with coincident tumour growth, the one a fibromyoma uteri, the other an adenoma of the kidney.

This statement is not very convincing, indeed, arguing on similar lines one might assert that the disease is of much more frequent occurrence in this decade than previously. Probably the real reason is that formerly the malady was not so well known and was therefore only diagnosed in well-marked cases and in advanced stages of the disease; now with the aid of the Röntgen Rays it can be detected early and cases are thus reported sooner. In all cases in which malignant disease supervened, as Paget pointed out, it is only after a chronic progressive course lasting years that a tumour manifested itself, and as most of the cases reported since 1902/

1902 are still living, or at least have not been reported on further, one cannot tell in how many malignant developments may still occur.

In this connection the following letter in the "Lancet" 1909 (found only after this thesis was finished) is interesting as in it Dr. Roger Williams suggests as a new vista of medical research on Paget's disease the very theory which we have endeavoured to formulate.

THE NATURE OF OSTEITES DEFORMANS (PAGET) AND ITS
RELATION TO MALIGNANT NEOPLASIA.

To the Editor of the "Lancet".

"SIR, - In endeavouring to determine the natural relations of a novel morbid condition for which a definite place has not yet been found in our nosological cadres a great deal depends on the standpoint from which the pathologist surveys the scene.

Having for many years taken special interest in "osteitis deformans" (Paget), chiefly with the object of determining its inter-relations with malignant neoplasia, it will perhaps interest your readers to know the conclusion at which I have/

have arrived, after having studied the malady from this somewhat unusual standpoint. It will be remembered that three of Sir J. Paget's five cases were complicated by malignant neoplasia, and so many other examples of this concomitancy have since been reported that the impression has arisen that this form of bone disease is often complicated by other tumour formation. This being so, I was much surprised to going over the records of over a thousand consecutive cases of primary malignant tumours to find that not a single one of them was complicated with "osteitis deformans". In endeavouring to unravel this puzzle I was led to pay particular attention to the precise seats and nature of the tumour lesions in cases of this concomitancy, and it then became manifest that these affected chiefly the skeletal bones, and that they were generally described as being of "sarcomatous" nature, many of them having a myeloid structure.

From these and other converging indications of like import I became convinced that the neoplastic disease not uncommonly associated with "osteitis deformans" is something quite distinct from the ordinary carcinoma and sarcoma. Further examination of the ensemble of the subject in this light/

light convinced me that the real affinity of the concomitant disease in these cases is with "multiple myelosis" in its minimal form, whether associated with albuminuria or not.

In conclusion, I think it would be as well if future investigators of "osteitis deformans" were to conduct researches along the lines I have indicated, as a new vista would thus be opened up.

I am, Sir,

Yours faithfully,

Sgd. "W. Roger Williams."

HISTOLOGICAL/

V. HISTOLOGICAL CONSIDERATIONS.

For the sake of clearness before describing the histological appearance we define the use we will make of the following terms, which we shall frequently employ.

1. METAPLASIA. Development by cells which have been accustomed to produce one particular order of tissue of another but equal order.

2. KATAPLASIA. Development by cells which have been accustomed to produce one particular order of tissue, of a tissue of a lower order representing an imperfect stage in the development of the said tissue.

3. ANAPLASIA. Depression of the differentiation capacity of cells accustomed to produce a particular order of tissue, accompanied by increased vegetation capacity, so that those cells have lost the power of producing the fully differentiated tissue (and are incapable of regaining it) when, at the same time they exhibit increased energy of growth.

As/

As an aid to this discussion of the relationship between Paget's disease and neoplasia it is essential in the first place to determine what is the order of histological change that characterises the disease.

Are the changes of an inflammatory nature?

Here we would emphasize that Paget distinctly stated that the name "osteitis deformans" was provisional. He was not sure that he dealt with an inflammatory manifestation, some name was necessary and he suggested the use of this term until the real nature of the condition was revealed. Butlin, von Recklinghausen and Stilling all upheld the inflammatory nature of the process. More recent writers are coming round to the opposite opinion of metabolic disorder.

We would lay down forcibly that histologically what must impress whoever studies the lesions of Paget's disease is the remarkable absence of any of the signs which we usually associate either with an active or a past inflammatory process. The periosteum over the affected bones is neither thickened, nor adherent/

adherent: it is neither the seat of infiltration nor of fibrosis. The changes in the bone itself are not of an inflammatory type: there is neither intense congestion, nor small celled infiltration, now, on the other hand, perivascular fibrosis or dense general fibrosis of the medullary spaces.

On the contrary the picture is that of an atrophic state, or perhaps more accurately of a tissue regression. In the bones which outwardly show no change, as in the section of the metacarpal (fig.1), we are struck by the appearance of simple atrophy of the bony elements. The compact surface bone is so diminished in amount that in places it has completely disappeared: the more internal bone trabeculae are thin and shrunken, separated by wide marrow spaces. What bone is left is of normal structure, showing, however, but little evidence of the recent formation of new superficial laminae seen in normal bone. The osteoblasts lying on the bone are few and so shrunken as only to be recognisable after somewhat careful search. The marrow elements consist of fat cells and little else beyond delicate walled vessels: other cell elements are strikingly absent. The changes are those commonly associated with advanced senile atrophy.

These/

These are not, it is true, the most characteristic changes, those that we regard as typical. Such are found in the long bones, but in them the changes are of the same regressive order. In them there is the same deficiency of bone elements proper. What bone is present is in the form of thin irregular trabeculae separated by singularly wide marrow spaces. There is a singular relative absence of osteoclasts in the sections of the humerus in our case. Field after field may be searched - and this under the low power - without encountering one, although in the clavicle they are more frequent. This indicates either that the absorption of the bone is a singularly slow process, or that we deal with the results of a past process of active absorption. The appearances are wholly unlike what is seen in osteomalacea with its deposits of laminae of non-calcified bone material. Here absorption of the bony matter is the predominant feature. The marrow is equally remarkable. There is practically complete absence of lymphoid and what we may term myelocytic elements. There is an absence of fat cells: at most here and there what appear to be dissolved out shadows of fat cells or small collection of the same may be observed, the subjects, it would seem, of serous atrophy, (Fig. 4). The marrow proper/

proper is replaced by a delicate somewhat oedematous fibrous tissue - the "Fasermark" of von Recklinghausen, & Rehn (Fig. 2.). Here and there irregular small clusters of cells can be seen in this, (Fig. II, 7). Careful study shows that these are of the same order as the osteoblasts.

We have here all the signs of progressive atrophy of the affected bones coupled with what we may term a fibrous metamorphosis of the marrow.

Studying this fibrous tissue development more carefully we find that the one tissue element still present is the osteoblast. As noted by several previous observers, while over many of the lamellae these are shrunken and inconspicuous, in several areas they are relatively abundant forming a characteristic cell layer lying upon the surface of the bone, (Fig. III, 2). While so frequent here, study of these regions shows a curious absence or at most paucity of new underlying bone formation, (Fig. III, 4). Such formation is not the exception, not the rule. It may, however, be noted in several places that around these is a fibrillar deposit. The individual osteoblasts lie against the bone and are surrounded on their free aspect by fibrils, which are adherent to the bone (Fig. II, 8) passing out at right angles into the marrow, and the fibrous marrow is composed of/

of similar delicate fibrils and bundles of fibrils, in part originating from these osteoblasts lying against the bone, in part from cells of osteoblastic type free in the marrow spaces, (Fig. II, 7).

There is evidence here, in short, of an anaplasia or kataplasia of the osteoblasts whereby now their function is diverted from the higher plane of forming bony matrix to the lower plane of simple connective tissue development in the marrow. Evidence, to repeat, not of an inflammatory, but of a regressive, kataplastic process.

This is no new theory, although it may be expressed according to a more modern terminology. Lunn in 1884 in discussing a case of Paget's disease which he was reporting, raised the question as to what was essentially the nature of the morbid process. He concluded that Paget's view that it was a chronic osteitis was untenable unless "too elastic use was made of the term 'inflammation'". There was no associated fever or periostitis and anatomically the appearances were not those of inflammation. He went on to say that in Paget's disease the growth of the new bone may become so active as to burst through all restraint and to result in tumour formation. His views were that it was a constitutional disease producing atrophy and absorption of a large part of the/

the osseous system, consequent weakening of bones and bending, compensatory strengthening by the growth of what may be looked upon as a variety of callus, occasional formation of definite tumours, and finally a fatal cachexia.

Goodhardt also, who in 1879 reported several cases, was of the opinion that Paget's disease was a generalised form of tumour of bone and not an inflammation. His grounds for holding this view were -

"that in the reported cases of associated malignant disease with Paget's disease, the tumour formation was not by any means always in the bones: a point altogether against the evolution hypothesis of chronic inflammation turning into cancer, and in favour of a tendency on the part of many tissues to overgrow".

He pointed out that two processes were at work in Paget's disease, first a chronic hyperplasia lasting over years: the other so active as to lead to a spontaneous outburst in many parts with great rapidity, under such circumstances very little hyperostosis could occur.

VI./

These views of Goodhardt (to a large extent) which we only encountered after we had arrived at our own conclusions, are strikingly in harmony with those conclusions. What struck us especially in the study of the amputated limb of our case was in the first place the obvious existence of tumours (see photo, Fig V.), in the second place the relationship of those tumours to the bone in which they originated. Had we to deal with ordinary discrete tumours, we should have expected to find well marked evidences of centrifugal growth. That in one of the tumours there was such evidence, i.e. of sarcomatous infiltration of the periosteum, we shall discuss later. But as towards the shaft we should have expected to find either that the growth was well defined with a clear limiting zone between the new growth and the pre-existing bone or on the other hand, if the growth were more active and malignant, evidences of infiltration of the pre-existing bone by the tumour elements. If, that is, the growths were of the osteoid or osteosarcomatous type (and they were clearly bony) then the older, more central parts of the tumours should be bony, the younger more peripheral, infiltrating parts, should be more cellular, advancing into and eroding the pre-existing bone of the shaft. There was not a sign of any such process. On the contrary, in place of such uncentric centrifugal growth the appearances are such as can only be translated as being due to a progressive and diffuse assumption of increased growing powers on the part of what we have above described as the kataplastic osteoblasts/

osteoblasts of sundry regions, as (to employ Dr. Adami's terminology) a blastomatoid rather than a blastomatous development.

We would especially call attention to fig. IV as illustrating this point. In it we have part of a section from the shaft of the humerus, stained by van Gieson's method and seen under a low power. It is seen that the marrow in the main is of the "Fasermark" type, characteristic of the pure Paget's disease, but here and there in direct connection with the bony trabeculae is the development of an osteoid network taking on a deeper more crimson-lake stain with the dye, and under the high power much more translucent than the bone tissue proper. This osteoid framework springs directly from the bone, i.e. is laid down by the osteoblasts there in situ. We cannot conceive such a development as due to the infiltration and invasion by elements advancing from the tumour at the head of the bone.

The tumour growth at the head of the humerus besides this increased osteoid tissue shows undoubtedly new production of small trabeculae, indeed there is a zone of this new formation occupying, as it were, the region of the absorbed compact shaft and expanding from this. Even at other regions (as/

(as at IV 3) where the osteoid development occurs away from the trabeculae and in the middle of the marrow spaces, the osteoid network continues almost imperceptibly into and gives place to the surrounding connective tissue fibrils. There is no sharp demarcation of either cells or matrix, but a gradual transition such as can only be possible from an actual transformation of the cells of the part, or modification in function on the part of the same. Infiltration and replacement could not possibly give origin to these appearances. We can only explain the appearance by assuming that over a large area of the upper end of the humerus (and the same holds for the other bones, the seat of the new growth) the osteoblasts, already modified, or kataplastic to the extent that now they tend to form a fibrous marrow rather than bone proper, tend diffusely to undergo still further modification in function and now with evidences of more active growth give origin to an osteoid, fibrohyaline, rather than to a fibrous matrix.

What leads to this alteration in function we do not pretend to say. At most we would lay down that it is another evidence of the association of modified function and growth. Von Recklinghausen and/

and Rehn regard the new growth in this and the allied osteomalacia as secondary to traumatism of a moderate grade, pointing out that it is in those bones most subjected to insult that the growths are liable to appear. For ourselves we cannot help suggesting that there is something reactive in the process, an endeavour, if we may so venture to express it, to form something which if not true bone is nearer thereto than is the Easemark, a form of internal callus, acting as a splint for the greatly weakened bone. But we confess that such views are purely teleological and scarce worthy of mention. It is sufficient for us to emphasize that from the very nature of the tissue we are here afforded an absolute demonstration of the existence of blastomatoid growths, - of growths due to the diffuse and coincident involvement of the elements of a tissue in a neoplastic process rather than to the heaping up of the descendants of an individual cell or of a few cells, such as we presume are implicated when a "cell-rest" becomes the origin of a neoplasm.

We shall later, in discussing the extent of blastomatoid neoplasia, refer to Max Landau's somewhat parallel study of a case of gliomatosis. In that Landau arrives at a compromise. According to him, /

him, not all the glial cells of the regions involved take an active growth, but only certain of them (Trabenzellen) in intimate relationship with the ganglion cells, or neurocytes. He would hold that in such cases we deal with abundant primary centres of new growth, instead of a few: in short, that the difference between the ordinary blastoma and the diffuse blastomatosis is merely a difference in degree. Certainly we freely admit that in our case it may be urged with justice that the modification in cell properties which is the beginning of new-growth shows itself at multiple foci, that in fig. IV, for example, obviously some of the osteoblasts are affected, others are not, some continue to produce or control the production of fibrils, some, only, to determine the development of the fibro-hyaline osteoid matter. In another portion of the section of the metacarpal bone that afforded fig. I, it is interesting in this connection to note that there were minute areas of osteoid metamorphosis of the bone marrow, evidently very recent. But this multicentric view would seem to deny or oppose the conception of successive modification of the osteoblasts in a given area until practically all exhibit the new characters, and to demand that the growth/

growth proceeding from several centres involves and replaces the intervening more normal tissue. Now, nowhere in our sections (so long as the growth remains within the bone) have we encountered any indication of multicentric growth of this order. On the contrary, the indications are of progressive enlargement of the involved area by the metamorphosis of cells at the periphery. Whatever the cause of the metamorphosis, it influences progressively a wider area of cells, and it is by this process of metamorphosis of previously unaffected cells and not by infiltration and replacement - by a process totally different from the mode of enlargement of the ordinary blastoma that the neoplastic development undergoes extension. It seems therefore useful, not to say necessary, at the present moment to emphasize the difference in the mode of development of these two orders of tumours, rather than to endeavour to regard them as different manifestations of a common process.

In stating this we by no means wish to imply that once the cells have undergone this kateplasia they do not exhibit active powers of growth. As shown by fig. VI (stained by Mallory's stain) the new osteoid tissue is abundantly cellular.

Studying/

Studying what we believe to be the transition from the areas of Fasermark to this osteoid tissue we are struck by its abundant cellularity. In the fibrous marrow in general, the cells are few and far between, save as already noted, here and there in immediate apposition to the bone and to a less extent around certain vessels.

We would emphasize that in our sections around the blood vessels in the marrow, these cells occurred in relatively large numbers surrounded by "Fasermark", and this again surrounded in an orderly manner by osteoid tissue. The transition is associated with a greater vegetative activity of these osteoblastic cells. The matrix in which they lie exhibits at first merely a loose fibrillar arrangement. Almost imperceptibly this takes on a deeper red stain by Van Gieson, or blue stain by Mallory, and so now the transition can be traced from fibrillar to a hyaline but still fibrillar osteoid matrix. Even where this is well developed it remains abundantly cellular (vide fig. VI). That figure does not perhaps indicate as well as might be wished that in the main we deal not with a solid intercellular matrix, but with a network of now delicate, now thicker hyaline bars, (VI 1.).

This/

This network encloses or in part surrounds either single cells, or clusters, which from their arrangement would seem to be undergoing proliferation (VI 3). Unfortunately our material has not been so preserved or so stained as to demonstrate mitoses. We see, however, the result of this proliferation and growth in the increased breadth of the medullary spaces between the bony trabeculae, and in a general swelling of the bony shaft, with formation of a tumour upon that shaft, a tumour formed of this osteoid growth. With this overgrowth there is a reproduction of (imperfect) bony tissue. Namely as shown in fig. VII (as also at 2, fig. VI) in certain areas, in place of osteoid trabeculae there develops a continuous hyaline matrix wholly enclosing individual osteoblasts, and in parts as shown in fig. VII the deeper portions of these more concentrated areas exhibit an imperfect calcification. There is, in short, the formation of osteoid trabeculae.

In this way the bulk of the tumours, such as this seen in the photograph, fig. V, is formed of osteoid tissue, distending and spreading apart the original bony trabeculae and what is more growing in direct association with the same. We have/

have the development of what, according to ordinary nomenclature is an osteoid sarcoma, but what from the mode of growth is more correctly termed an osteoblastomatoid state. Over the bulk of the tumour the growth is purely local, is not infiltrative and respects the natural boundaries of the organ within which it grows. In none of these features does it comply with our ordinary conception of sarcoma.

Nevertheless, in one of the multiple tumours there has at one region developed a truly sarcomatous area, and it is interesting to follow the successive changes, as exhibited by figs. VIII, IX and X. We here described the successive stages observed.

This growth is towards the upper end of the tumour and towards its outer surface. Fig. VIII exhibits what may provisionally be described as the first stage. In this at 1 we observe one of the outlying osteoid trabeculae in which there has been an imperfect deposit of calcareous salts in the deeper portion: to the left of the diagram and above is shown the osteoid marrow, the spaces containing either one or numerous cells. The fibrillar framework or structure of this osteoid tissue can be distinctly seen in many parts of the figure. At 3 and/

and 4 are to be recognized the transition from fibro-hyaline to purely fibrillar matrix, so that in the lower portion of the figure there is present a loose cellular structure presenting an equally loose fibrillar network. The cells are irregular in shape, tending, on the whole, to be somewhat spindle shaped, with oval nuclei. In many places these cells can be seen to possess processes, or, in other words, to be continued into fibrils (VIII, 6) which fibrils enter into and contribute towards the fibrous stroma. Here and there, as at 5, there are small areas or islands of hyaline deposit in this stroma. Fig. IX shows an area somewhat further out. Here over considerable areas anything of the nature of a hyaline osteoid matrix is wanting. There is a more richly cellular growth, the cells as before being irregular, but roughly of the short spindle celled type, and between them is a loose, irregular fibrillar stroma, the fibrils tending to run in rather coarse bands which are cut in various directions. We have here, in short, the appearances usually described as fibro-sarcomatous. This portion is close beneath the periosteum. Fig. X is of distinct interest: it is taken at what is clearly the periosteal boundary of the growth, the dense/

dense series of layers of coarse bands of connective tissue which traverse the figure being periosteal, (Fig. X 1). In the upper portion at 2 is the growth within the periosteum presenting the characteristics noted in the preceding section. But the clear evidences of infiltration of the periosteum, in the shape of small collections of cells in between the fibrous bundles, become more abundant on the outer aspect and there cause a wide separation of these bundles, and immediately outside at 3 there is an almost purely cellular growth with little or no evidence of a fibrillar matrix, a growth having the characters of a mixed-celled sarcoma, short spindle-celled forms predominating. We have here a true sarcoma, true both in its histological and in its infiltrative characters.

How are we explain or picture the progress of events in this case? It is deserving of note in the first place that the transition is not narrowly focal; just as towards the shaft we observed a diffuse transition from fibrillar to osteoid matrix, so here the appearance exhibited in Fig. VIII is to be seen over a considerable area.

Two views may be taken regarding the process as it has occurred in this region. On the one hand/

hand we may hold that in the subperiosteal region, towards the head, there has been an area in which the marrow has remained fibrocellular, with active proliferation of osteoblasts and that the progressive growth of the tumour has been due to the gradual conversion of the deeper portion of such an area into osteoid tissue, that, in short, fig. VIII represents, not so much a regressive as a progressive stage, represents the gradual conversion of the "Fasemark" into osteoid tissue. Holding this view, we must suppose that the vegetative powers of the subperiosteal tissue have become more and more active until now this very vegetative activity has led to infiltration of the periosteum and true infiltrative sarcomatous growth outside the periosteum, accompanied by further anaplasia.

Or, on the other hand, we may regard the osteoid tissue as the older, and translate the appearances here seen as due to a further anaplasia of the osteoblastic cells, so that now at the same time that they have gained more active powers of proliferation they have lost the capacity to control a deposit of a hyaline matrix, at most retaining the power of forming delicate fibrils. We may hold further that so long as these cells with their active vegetative powers remain in their normal/

normal environment, within the periosteum, they manifest this power of fibrilformation, but that now through the very activity of their proliferation certain of them grow into and through the periosteum and gaining a new environment there, they suffer a further anaplasia, become even more undifferentiated, and take on all the characteristics, both histological and functional of sarcoma cells.

It is difficult, we confess, to convince ourselves absolutely which of these is the correct explanation of the appearances. It is difficult, we freely admit, to regard the primary conversion from fibroid to osteoid marrow as evidence of anaplasia and the very reverse condition of conversion of hyaline to fibroid marrow as similarly anaplastic. One or other of these processes is anaplasia, but certainly not both. It is thus that we have employed the term "kataplasia" for the first of these processes, suggesting thereby that while the cells are retrograde, they still have retained certain adaptive or metaplastic powers and capacity for higher differentiation. We regard, that is, the osteoid marrow as a higher differentiation than the fibroid marrow. But, on the whole, we are inclined to decide against the first/

first of the alternatives above mentioned, on the general grounds that elsewhere in our sections we find no evidence of the existence of a subperiosteal proliferative layer of cells: no evidence that the tumour has grown by peripheral accretion, but rather everything points to a generalized and diffuse development of the new osteoid tissue: and, thirdly, this conception of the persistence of an actively proliferating superficial layer is contrary to what we observe in other blastomatoid states, as again in other cases of benign multiple bone tumours. Time and time again we have had the history that the tumours remain benign and respecting their natural boundaries for, it may be, long years, and only after the expiration of long periods is it observed that in one or more of the tumours certain localities take on definitely sarcomatous and infiltrative properties.

The history is wholly against the supposition that in these tumors there have been present from the first cells of the extreme vegetative sarcomatous type; it is wholly in favour of the conception that after growing at a slow rate over long periods and possessing differential properties, as the tumour gets larger and larger, whether from alteration//

alteration in nutrition or in environment or tension to which they are subjected, certain cells undergo further "Entdifferenzierung" become more anaplastic and assume malignant properties. On these grounds, therefore, we incline to the second alternative. But which ever view be held, the fact remains that studying this area of transition, we find no evidence that we deal with the sudden assumption of excessive growth powers by the descendants of one or a few cells, no evidence of centrifugal growth from individual foci, but, on the contrary, a fairly diffuse anaplasia over a considerable area, numerous cells subjected to similar environmental influences exhibiting the same tendency towards increased and anaplastic proliferation.

VII. BLASTOMATOID GROWTHS OF OTHER TISSUES.

Almost everyone of the connective tissues may suffer from a diffuse overgrowth either localised or general of one of its cell elements.e.g.

Lipomatosis exostosis and echondrosis, lymphomatosis, neuromatosis, neurofibromatosis, it may be well to summarise the characteristic features of these before comparing them with Paget's disease, with which they will be found to have many features in common.

LIPOMATOSIS: A diffuse overgrowth of adipose tissue which may be regional or general, not clearly defined from the surrounding tissue and which may exhibit some what illdefined areas of more closely congregated fat cells.

The disease is one of middle life, the onset is insidious, the course is a chronic progressive one and is associated with debility, psychic phenomena neuralgic pains may be a prominent feature (adiposa dolorosa) Trophic changes in the skin, (pigmentation, varix and also frequently associated arthritic conditions. The etiology is obscure, the condition often seems to come on after a traumatism. The hereditary tendency is marked, Lyon out of 20 cases had eight with heredity history.

In/

In the later stages sarcomatous changes may occur.

Lyon in his brilliant monograph on the subject points out the evidence in favour of the condition being due to disturbance of internal glandular secretion. The tumours when present tend to be multiple, and are never clearly defined from the surrounding tissue. Cachexia may supervene and death.

NEUROMATOSIS AND NEUROFIBROMATOSIS: von Recklinghausen's Disease. A rare disease usually occurring in early adult life, characterised by multiple small fibrous tumours arising in connection with the nerve sheaths, in the subcutaneous tissue, along the course of the peripheral nerves, and sometimes even in the central nervous system. These show a marked hereditary tendency 20% of cases (Lyon). The condition may come on after trauma, any slight injury during the course of the disease leads to rapid proliferation of the tumours. Associated with these there is pigmentation of the skin, tendency to varix and ulceration and often psychic phenomena, (Elephantiasis may be associated with von Recklinghausen's disease) Ribbert, Rolleston and Austin, etc. report cases with an associated sarcomatous change in typical examples of von Recklinghausen's disease. The disease may be localised to the branches of one nerve plexus.

In/

In the later stages of the disease cachexia may supervene.

PATHOLOGICAL ANATOMY OF VON RECKLINGHAUSEN'S DISEASE:

There has been a long debate as to the exact nature of this overgrowth, whether it is purely fibromatous, or, as von Recklinghausen pointed out, a neurofibromatosis. As pointed out by Adami, the recent researches of Verocay (Ziegler's Betrage, 1910) and those to a certain extent of Durant (see ref. in Adami's pathology) show that the parenchymatous overgrowth is really a diffuse overgrowth of cells from the sheath of Schwann, which like the glia cells are of neuroblastic, and not as has been generally held, of mesoblastic origin.

A study of the tumours, whether along the course of the larger nerves, or subcutaneous, shows that here again there is no sharp definition, the tumour passing imperceptibly into the unaffected nerve sheath elements, but like the other blastomatoid conditions while distending the sheath or boundary it is still covered by the external perineuron and does not infiltrate the same, save where one or other of the multiple tumours takes on a sarcomatous change.

(Compare the development of blastomatoid tumours/

tumours in fish. Gaylord.)

GLIOMATOSIS: A diffuse new growth arising from neuroglia cells in the brain or spinal cord, in many cases there is a strong heredity tendency. The onset is insidious the disease runs a fairly chronic course, one to three years, in many cases there are surprisingly few nervous symptoms. There may however be the usual signs of intracranial tumour, but owing to the diffuse nature of the new growth and the fact that multiple gliomata are of frequent occurrence, localisation is often impossible. The tumours are not sharply defined from the surrounding tissues, in many cases they go on to sarcomatous development. Max Landau has recently published an extremely interesting research on a case of multiple diffuse gliomata (gliomatosis). He made an exhaustive histological examination of the various parts of the tumour especially of the borderland zones where the tumour merged into the surrounding tissue. His results throw light on the nature and mode of development not only of this particular tumour but probably also with slight variations, on that of other diffuse new growths. If we describe his findings and conclusions somewhat in detail it is because they seem to have some bearing/

bearing on our subject to which we will revert later.

Landau found on examining his case that it was impossible even microscopically to find the point at which the tumour ended and the normal brain tissue began. The tumour gradually merged into the surrounding tissue and in no section could he find any sharp contrast between the two, rather there seemed to be transition from the one to the other. By studying in detail numerous sections from the borderland region he was able to follow the various transitions from the central sarcomatous like neoplasms to the surrounding apparently normal brain tissue. He found first that in the tumour the ganglion cells were still present with their normal position and relation to one another unchanged; on going further into this he was able to find a region in which around these ganglion cells little groups of cells were found with darkly staining nuclei and small amount of protoplasm; these he called "trabantzellen" (e.g. Satellite cells) As one approached the tumour proper these increased in number and size becoming larger with clear protoplasm and bigger nuclei. Nearer still to the neoplasm these cells had the appearance of epithelial cells/

cells = (epithelioid cells of other writers). This was chiefly due to their arrangement in columns between the ganglion cells and to the very rudimentary condition of their processes. Round the vessels, which were in these areas more numerous, Trabenzellen also occurred, and rapid cell proliferation ensued (compare our case of Paget's disease.) The walls of the small vessels underwent calcareous degeneration, while the vessels at the base of the brain were quite free from atheroma. Finally on nearing the centre of the tumour it was found that the tumour cells now consisted of large masses of round or oval cells with poorly developed processes and large nuclei, while the calcareous ganglion cells were still present in their ordinary numbers and between the tumour cells axis cylinders were still seen to run.

Landau found exactly the same stages of the process in the other smaller tumours in the basal ganglia and he concluded as follows:- First, in the glioma the normal structural relationship of the ganglion cells and axis cylinders is preserved, a tumour which had arisen from one point from an embryonic "cell rest" would have supplanted and destroyed these, therefore the condition cannot be caused by such a tumour.

In/

In many parts of the tumour are found distinctly malformed glia cells "epithelial-like formations" which denote a stage of development of the tumour cells not isolated cell rests; these are merely young tumour cells and not epithelial.

The tumour elements are in general characterised as poorly differentiated glial cells with imperfectly developed processes. The tumour cells exercise a necrotic and calcifying influence on the ganglion cells and vessels lying within their domain.

He specially noted the absence of definition of outline and of signs of infiltration in the tumour, also the evidence of primary multiple growths and concluded that the tumours arose in situ from "just as many primary foci as there were ganglion cells in the part."

He admitted that there must be some general abnormality of the cells of the tissue, probably a hereditary constitutional instability of cell so that some unknown cause was able to stimulate it to abnormal growth.

(Compare our case of Paget's disease on page)

we have pointed out that Landau's view that there are as many separate gliomata as collections of glia cells/

cells around the ganglion cells, is to say the least, unnecessary, and the very fact that at the periphery of the growth he finds this progressive taking on of anaplastic or metaplastic change by these particular groups of glia cells, shows that here (as in our own case) we deal with some continuously acting influence in what previously had been normal cells, leading to a gradual extension of the morbid state of a totally different order to that which we are accustomed to conceive as being in action in the development of the ordinary unicentric or pleuricentric blastoma or true tumour.

LYMPHOMATOSIS/

LYMPHOMATOSIS: Hodgkin's disease. It may seem questionable whether this disease should be included here, as of late years there has been a strong tendency to regard it as one of the granulomata.

(Lymph granulomatosis of Fraenkel, Much, Chiari, Reid, etc.) The disease has so many points of similarity with the others we are grouping together that we feel justified, however, in putting it at least temporarily among the blastomata conditions. The disease which is a rare one, usually occurs in early adult life.

It is characterised by general progressive enlargement of the lymphatic glands and lymphoid tissue of internal organs (spleen,). In many cases changes are described in the bone marrow.

The spleen is strikingly enlarged and on section shows small areas of lymphoid tissue studded throughout the substance ("Hard-bake spleen"). The course of the disease is as a rule a chronic one, the onset is insidious, the first glandular enlargement takes place in the posterior cervical region. There is an associated tendency to pigmentation of the skin, trophic changes, (varix, ulceration, etc.), and more rarely, joint lesions, (e.g. arthritis) may occur. There may or may not be associated blood changes./

changes. In some instances the disease may have an acute course, irregular fever, rapid glandular enlargement, weakness, cachexia and death.

There is a marked tendency to sarcomatous change with infiltration of the adjacent tissues, e.g. vertebrae eroded, vessels thrombosed.

Pappenheim describes the condition as a "hyperplasia of the lymphoid tissue throughout the body with a pernicious course."

Fabian in a treatise on this subject described the changes as firstly, a lymphatic hyperplasia. secondly. the formation of a polymorphonuclear granulation tissue, thirdly, fibrohyaline degeneration."

A not infrequent accompaniment is amyloid degeneration. Fabian points out that the commonly benign process may encroach itself infiltratively on the neighbouring tissues, resulting in a lympho-sarcomatous growth with transition into sarcoma especially in the mediastinum.

Pathological appearances of the glands differ according to the stage of the disease; at first soft, they tend to become firmer with age and gradually enlarge; there is no tendency to break down /

down and suppurate and for long they may remain discrete. The blood picture is not characteristic, there may or may not be leucocytosis; there is a tendency to skin disease.

Pathological appearances: The glands contain a varying amount of fibrous tissue according to the stage; the cells are chiefly of the small lymphocytic type and multinuclear giant cells also occur in large numbers; eosinophiles are frequently seen.

The microscopic appearances and also the clinical course of the disease suggested to many observers that it was probably a form of tuberculosis; the tuberculin reactions, however, have in many cases given negative results. One author in five out of eight got negative tuberculin reactions. In many autopsies no evidence of tuberculosis could be found. In some cases both conditions were present, but even then the evidence does not tend to prove that they are in any way related. Guinea-pig inoculation has had negative results.

Syphilis has been suggested as a cause. However, in all the cases which have been tested, the Wassermann reaction has been negative. Bacteriological research has not so far elucidated this question. Frankel and Much have just published an interesting/

interesting account of 13 cases, in 12 of which they isolated by staining by the anti-formine method small granular rods, Gram positive but not acid fast, which they claim to be morphologically like the non-acid fast variety of the tuberculosis virus and yet distinct from it.

The organisms, they state, were very few in number, they claim they are not tubercle bacilli, animal experiments were negative, cultures were negative.

Chiara examined the glands in his case by this method but his results were negative. We have had an opportunity of studying a case of this disease and following the exact description of Fraenkel and Much's methods; (as a control a known tuberculous gland was used.) In this the tubercle bacilli stained as Gram positive granular rods by the anti-formin method. The Hodgkin's gland, however, showed no such rods, merely here and there an amorphous granule or two were found, but having no even size or regular grouping to lead one to a positive diagnosis. Comparison of these ill defined granules with the distinct tubercle bacilli made one without hesitation decide that the result in the Hodgkin's case was negative. Authorities like Sternberg./

Sternberg, Chiari, Schwenkenbacher and Fischer, etc. all agree on the non-tuberculous character of the condition.

In the later stages the glands become fibrous and cicatrised. In many cases, however, the process may go on further and the growth infiltrate the surrounding tissue breaking through the capsule of the gland. Chiara reports a case with a mass in the mediastinum the size of a child's head the lung being infiltrated by the growth and a bronchus surrounded by it. The Pleura in this case was also studded and several arteries had their walls infiltrated. In one of Fraenkel's cases there was infiltration of the ureter, bladder and vertebrae.

It is possible to bring evidence from sundry regions of the body in which chronic inflammatory states have been followed by the development of malignancy. This fact, therefore, that Hodgkin's disease does at times exhibit areas of sarcomatous disease is not of itself a convincing argument that we deal here with a blastomatoid state.

It must, however, be admitted that the other features of the condition of the disease are such as approximate to the other blastomatoid conditions, and that being the case, the occasional tendency/

tendency towards sarcomatous change may be quoted as another argument in favour of this contention.

In only five out of 13 autopsies was the bone marrow examined and in all these cases it was found to contain numerous lymphoid masses. We would suggest that until more conclusive evidence of the injective nature of the disease is found, that it might be classed with the other blastomatoïd conditions, the generalised diffuse overgrowth, the tendency to malignant disease, the insidious course, the frequent trophic changes in skin, etc., all show a resemblance to other members of this group.

LEUKAEMIA/

LEUKAEMIAS AND PSEUDO-LEUKAEMIAS.

It is beyond the scope of this thesis to go in detail into the connection between diseases of marrow bone and the leukaemias, sufficient to say there is apparently a close relationship between them and many authorities believe that all leukaemias are of the nature of diffuse new growths the blood condition merely being a secondary symptom of the disease. (Parkes Weber, Pappenheim, Muir, etc.) Chloroma would form a connecting link between the two. We have endeavoured to show that Paget's disease is itself related to other diseases of the bone marrow which are due to generalised metaplasia of cell elements present in normal marrow.

The following classification by Parkes Weber (Jour. of Path. and Bact. 1903.) is interesting in this connection, "leukaemias and pseudo-leukaemias can be divided into 6 types :-

1. A new growth of lymphocyte like cells originating in the bone marrow, and not overflowing into the circulating blood i.e. Myelogenous Pseudo-leukaemia, lymphadenomatosis of bone multiple myeloma of lymphatic type. Lymphosarcoma.

2./

2. Similar to the above but the lymphocyte-like cells overflow into the blood stream, myelogenic lymphocythaemia : = acute leukaemia (?)
3. A new growth formed in large part of lymphocyte-like cells originating in lymph glands, spleen or lymphadenoid tissue generally into the circulating blood. Lymphatic or Spleen lymphadenoma. Hodgkin's Disease. (In the more chronic and fibrous varieties of this type the microscopic appearances differ considerably from acute cases.
4. Similar to the preceding, the lymphocyte-like cells invading the blood stream - lymphatic or splenic lymphocythaemia.
5. A new growth originating in the bone marrow from cells derived from the myelocytes and not invading the circulating blood i.e. Myelogenous Pseudo-leukaemia. To cases of this type, and to mixed cases of this type the term myelomatosis (multiple-myeloma) might be limited perhaps.
6. A new growth differing somewhat from the preceding and characterised by its myelocyte like cells overflowing or being drawn out into/

into the circulating blood, and by Bence Jones Albumosuria not occurring as it sometimes does in the last type - (5) - i.e.

Splenomedullary Leucocythemia -

According to this scheme one must regard the excess of W.B.C.S. in the blood in all kinds of leukaemia as due to an inroad of tumour cells from a hyperplasia like tumour formation in the leucocyte producing tissues of the body, all forms of leucocytis (including lymphocytosis) being merely expressions of some reaction in the tissues in question. A leucocytosis is therefore, strictly speaking, never an early stage of leukaemia; yet a true leucocytosis from any cause may perhaps sometimes be followed by true leukaemia in so far as the reactive growth in the leucocyte forming tissues, (of which reactive growth the leucocytosis is the expression) may be supposed to give a start to the kind of tumour formation (of which the leukaemia is the expression) just as chronic irritation of the skin sometimes acts as the exciting cause of epitheloma..

It is worthy of note that Muir writing on the etiology of leukaemias in Clifford Albutt's System of Medicine, says :-

"Is/

"Is leukaemia analogous to tumour formation? In certain cases tumours do actually occur. Then again as regards the duration of the disease, analogies might be drawn with tumours of different degrees of malignancy with corresponding variations in the type of cell. The chronicity of myeloid leukaemia, in which the most highly differentiated cells are in excess, and the comparatively undifferentiated or more productive types of the cells in most acute cases of disease.

Is leukaemic proliferation analogous to tumour growth? The analogy with tumour growth is in many respects close. If we imagine a condition affecting leucocytes in the same way as sarcoma affects the connective tissue cells, we might expect to get changes similar to those found in Leukaemia. At present we must speak with reserve as to the etiology. Most of the data bring it into close relation to tumour growth, but a toxic phenomenon is also present in many cases."

In/

In this association, without going into full details over these most suggestive observations, we would call attention to the rather striking frequency with which one or other of these Blastomatoid conditions involving tissue other than bone have been present in cases of Paget's Disease. It would almost seem as if there was a generalised instability of connective tissue cells in these cases, so that slight stimulus could produce metaplastic changes in them. Goodhart's case had associated multiple lymphomata of spleen, liver, etc., mediastinal glands, another case had elephantiasis, five cases had goitre, several had multiple lipomata, one had molluscum fibrosa, many had fibro-myomata uteri, etc.

GOITRE:-We have here included the condition of goitre. These have much in common with, if they be not truly Blastomatoid conditions. There is the same liability to hypertrophy, involving extensive areas of the particular tissue; the same liability in a certain proportion of cases for the mere hypertrophy to give place locally to infiltrative and malignant growth. There is the same history in a small percentage of cases of the disease being hereditary, and a tendency to allied trophic changes in the skin and other tissues. Gaylord has shown that in fish the thyroid carcinomata develop by a metamorphosis of the glandular tissue, the result of a polluted water supply. This/

This starts by a simple hyperplasia (which can be arrested and even cured in the early stages by iodine) and later goes on to carcinoma of the gland.

This is an excellent example of the metamorphosis from mere hyperplasia to neoplasia.

McGarrison proved that feeding Hindoos on the sediment from the water in certain regions where goitre was endemic resulted in the growth of goitre.

	MULTIPLE EXOSTOSES, & ECHONDROSES.	LIPOMATOSIS.	NEUROFIBROMATOSIS (NEUROMATOSIS.)	GLIOMATOSIS.	LYMPHOMATOSIS.	PAGET'S DISEASE.
Age.	Youth.	Middle age.	15 - 30	15 - 40	Early adult life.	45 - 70
Hered. Tendency.	+ +	+ +	+ +	+ marked	?	+
Duration.	Chronic	Chronic.	Chronic	1-3 yr.	Chronic. (may be acute form).	Chronic.
May be localised.	+	+	+	+	+	+
Tendency to Multiple tumour formations.	+	+	+	+	+	+
Tumours not sharply defined. " infiltrative.	+	+	+	+	+	+
Tendency to Sarcomatous changes.	+ +	+	+ +	+ +	+	+
Trophic changes. Arthritis.	+	+ +	+ +	+	—	+
Blood changes.	—	May be anaemia.	—	—	May be leucocy- tosis.	—
Urine.	—	—	—	—	—	—
Course	Progressive .	Progressive.	Progressive	Progressive	Progressive	Progressive.
Pain, Rheumatic or Neuralgic.	?	+	+	Headache	Sometimes	+

VIII. OTHER BLASTOMATOID GROWTHS OCCURRING IN THE BONES.

MULTIPLE EXOSTOSIS and ECHONDROSIS.

Small outgrowths of bone or cartilage which are never clearly defined from the matrix from which they develop, they tend to be multiple, there is a strong hereditary tendency; the tumours in many instances undergo sarcomatous change.

MYELOMATOSIS.

(Myeloma multiplex, Kahler's Disease).

Parkes Weber, describes this condition as a "diffuse new growth primarily involving the bone marrow, especially that of the vertebrae, ribs and sternum, frequently also the skull and long bones; affecting males more than females, and chiefly those past middle life". The disease nearly always remains limited to the osseous system, though by direct extension it may form outgrowths projecting from the bones. Owing to the absorption of the hard, osseous tissue, the bones become softened or friable, and are easily fractured. The onset is insidious and is characterised by "rheumatic" pains, a progressive kyphosis/

kyphosis, debility, and in the later stages intermittent fever and cachexia supervene. Anaemia is a frequent symptom, as owing to destruction of the bone marrow the blood formation is impaired. Hence Jones' albumosuria occurs in many cases. The course is not a very chronic one, most cases lasting six months to two years. Kahler's case, however, lasted eight years. The tumours may not be noticed during life. In some cases the new growth is quite diffuse and there are no localised swellings on the bones. In many cases there is an associated "rheumatoid condition" of the joints. The bones in which the new growths occur have themselves undergone a retrograde change. "The Haversian canals being irregular in shape and distribution, and having a fibrous and at the same time dotted structure, strongly suggestive of a reversion to a fibrous connective tissue" (Warrington and Bradshaw). In their case the lesions were, disappearance of osseous tissue and growth in its place of a soft vascular mass of undifferentiated round cells. The affected bones are usually irregularly thickened, softened and deformed. On section the cortex is found to be thin as paper and within is a pulpy substance, greyish-red in colour, with here and there masses of purplish-red material. These masses consist of round cells, densely packed together/

together, some with a granular protoplasm, large nucleus and chromatin structure, others a homogeneous protoplasm; all mononuclear. The leading characteristics of the condition are multiple diffuse new growths of cytoblastic cells, these show no signs of infiltration; no sharp line of demarcation from the surrounding tissue, no metastases, except occasionally lymph glands may be involved. Parkes Weber described two types, (1) one in which the bone marrow alone is involved and the cells are of the round mononuclear type with granular protoplasm, (2) one in which the growth consists of cells resembling large or small lymphocytes and which are possibly derived from the non-granular predecessors of the myelocytes. Aschoff and Wright both describe these cells in their cases as resembling closely plasma cells. All writers note the striking absence of anything pointing to a primary focus and observe that the tumour cells are found in the marrow spaces at some distance from the apparent margin of the tumour. Wright described in his case that it seemed clear that the tumour nodules had arisen by aggregation of the tumour cells in the spaces between the fat cells, which spaces normally contain the vessels, marrow cells and blood. Then by further multiplication of the tumour cells the fat and other cell elements/

elements of the spongy bone are obliterated.

Christian noted that in sections where the tumour and bone marrow about no sharp line of separation is present, but tumour cells are found intermingled with normal bone marrow elements and fat cells. Christian, Muir and others have noted vacuoles or globules in the tumour cells (? Are these the source of the albumosuria). They describe the tumour cells as having a finely granular slightly vacuolated basophile cytoplasm, the nucleus showing a tendency to a mural arrangement of chromatin, nucleolus and centrosomes; they therefore resemble plasma cells. This view is debated by others, who regard these as lymphocytic or myeloblastic cells. There are indications that more careful comparative study of these cases of multiple myelomatosis will indicate that we are dealing with overgrowths of more than one order, in some cases lymphocytes, in others, myeloblasts, in others the erythroblasts, take an active proliferation. At least, the diverse descriptions given by different authors indicate that there are different types of cell overgrowth that have come under examination. Parkes Weber explains the presence of the albumosuria as being due to some ferment made by the autolysis of myelocytic tumour cells and therefore not present in other tumours of bone.

Heuter and Aschoff both describe amyloid degeneration/

degeneration occurring in cases of myelomatosis and refer to the frequency of such a condition in Leukaemia and Hodgkin's Disease.

Some cases had involvement of the long bones and skull, in many, as we have already indicated, the diagnosis was only made post mortem, the tumours not being perceptible during life.

Seegelken has described a case of multiple myeloma of ribs and vertebrae where the tumour structure was composed of densely packed round cells and "irregular masses of spindle cells" in which were found "isles of cartilage" and small necrotic areas and which he diagnosed as chondrosarcoma.

This certainly is not an ordinary case of myeloma multiplex. The existence of spindle-celled areas and "islets of cartilage" shows that the osteoblastic tissue was involved. We are inclined to suggest that these "islets of cartilage" were areas of osteoid tissue - similar to that shown in our Fig. vi. If this be so we have the following possibilities:-

1. That the round-celled areas in this case were of myeloblastic origin and therefore this affords an example of mixed blastomatoid overgrowth of both myeloblastic and osteoblastic elements.

2. That the round-celled areas represent a still more anaplastic stage of the osteoblastic cells - and/

and that this therefore represents a more malignant stage of an osteoblastomatoid growth. (Against this, absence of heterotopic metastases).

Whichever the case, the case is atypical and presumably intermediate.

RELATION of PAGET'S DISEASE to OTHER DISEASES OF BONE MARROW.

O S T E O M A L A C I A.

There is a very close relationship between osteomalacia and Paget's Disease, strikingly different though the clinical appearance of well-marked cases may be.

In osteomalacia decalcification and absorption are the leading characteristics. As a result of this the bones become rarefied and softened; and are very easily fractured. Two types are described, Osteomalacia Fragila and Osteomalacia Cerea, but they merely represent two stages of one and the same disease. The bones are not increased in size, the compact bone is reduced to a mere shell, and the medullary cavity is enlarged and usually contains a number of pale yellow cysts. The bone marrow is fatty and oily, with small areas of red marrow studded about it. The bones most affected are the pelvis, vertebrae, ribs/

ribs and femora, more rarely, the other long bones. Kyphosis and deformity of bones also occur, but in striking contrast to Paget's Disease the curvatures are sharply angular. The disease occurs chiefly in women, (91%), usually between the ages of 20 and 40, it runs a chronic course and is liable to curious periods of intermission. Like Paget's Disease, the first symptoms are usually rheumatic-like pains in the legs and back and progressive weakness and gradual deformity of the bones.

Dock describes in detail the pathological anatomy. The affected bones have a mere shell of compact bone left beneath the periosteum; the medullary cavity is widened and contains cysts. The bone marrow is fatty with varying amounts of lymphoid elements. Microscopically in the areas with yellow fatty marrow the Haversian canals seem to be irregularly widened and to contain many cellular elements, eosinophiles being often present in relatively large numbers. In the red marrow areas there seem to be an apparent structure, the spindle cells being arranged in whorls round masses of giant cells. Bony spicules may be seen in these areas, the osteoclasts lying in spaces in them. In other places the marrow may be gelatinous in appearance, evidently the result of necrobiotic change in the above tissue. The cyst walls are made of fibrous tissue which is continuous with that of the surrounding marrow and the pigment in/

in it is evidently blood pigment not melanin.

Hart, in describing the changes in a case of osteomalacia with malignant tumour, agreed that it is not right to attribute the cause of the tumour to some local change, but rather that the tumour formation was the last link in the chain of pathological changes to be recognised as an exaggerated expression of the general disease. He pointed out that the morbid change which showed itself in general osteomalacia finds its further expression in the fibrous metamorphosis of the marrow which in certain areas, (owing to vascular or other changes), takes on a rapid growth of the fibrous tissue resulting in a sarcomatous development. There is a great tendency to haemorrhage in osteomalacia.

Hart's conclusions were, that alongside the rarefactive processes in the bones in osteomalacia hyperplastic changes occur which not only find their expression in the formation of the osteoid tissue, but also in specially predisposed areas may lead to definite tumours through the excessive growth of the marrow tissue. He doubted the inflammatory origin of the disease. The cysts so characteristic of osteomalacia Hart explained were of two kinds - (1) in the tumours = result of haemorrhage and myxoedematous change; (2) apart from the tumours, also the result of haemorrhage (contain haematoidin crystals), therefore/

therefore they are signs of softening and old sequelae, not primary signs of the disease. Since Fehling noted the beneficial influence of removal of the ovaries on the course of osteomalacia in some cases, and attributed the disease to some abnormality of their internal secretion, this mode of treatment has been carried out with marked success in many instances. Cramer pointed out there is no characteristic histological condition of the ovaries in osteomalacia; still, apart from this, there may be distinct alteration in the internal secretion. In many cases, however, castration has done no good, and in these other observers have pointed out the frequency of abnormalities of the thyroid gland. Tolot and Sarvinat collected 11 cases of osteomalacia associated with exophthalmic goitre (microscopic signs of hypersecretion).

Hönnecke believes that the thyroid and ovaries "work on the same material but in different ways". In 23 out of 33 cases he reported changes in the thyroid gland in osteomalacia.

Latzko also pointed out that probably a close relation exists between internal secretions of the ovary and the thyroid and thus an abnormality of one would naturally tell on the other.

Tolot suggests osteomalacia is probably only a/

disorders of
 a symptom which may be manifested by the different
 glands of internal secretion. Borst has suggested the
 use of adrenal extract may be attended with some
 success in treatment. Virchow and von Reckling-
 hausen consider osteomalacia an inflammatory condi-
 tion. The latter calls Paget's disease ostitis
 fibrosa, and considers there is a close relation
 between it and osteomalacia. He thinks the tumours
 and cysts are the first manifestation of the disease,
 and that the exciting cause is a mechanical one in
 both conditions.

INTERMEDIATE CASES. Schoenenberger, von
 Recklinghausen and Rehn, have all described extreme-
 ly interesting cases which histologically seem to
 combine the characteristics both of Paget's Disease
 of bone and of osteomalacia and which have all been
 associated with multiple giant-celled sarcoma.
 These cases have been reported respectively as "os-
 teomalacia with multiple giant-celled sarcoma",
 "ostitis fibrosa with multiple sarcomata," and
 "Paget's Disease with multiple sarcomata". All have
 a striking resemblance to one another. The tumours
 which were spindle celled with numerous giant cells,
 contained in parts fragments of bony substance, and
 at the periphery bony trabeculae were found in the
 tumour structure. Schoenberger emphasized in com-
 paring his case with the other two, the fact that
 the/

the definition of the individual small tumours from the surrounding tissue (which was always typical "fasermark"), is never sharp, the transition is always a gradual one. In Rehn's case, (it lasted for nine years,) only the shafts of the long bone were affected. There was rapid formation of multiple tumours with coincident deformity and weakness of the bone. The tumours consisted of long spindle cells grouped around the periphery and in the centre masses of giant cells. The bone apart from the tumour was abnormal; there was no distinct compact outer part of the bone, which was merely composed of an irregular spongy tissue which cut easily with a knife; not only the bones which contained tumours but also the other bones showed this appearance.

The bone marrow apart from the tumour contained fine trabeculae of bone with osteoid margins. The reticular spaces were largely filled with a delicately fibrillated tissue of long spindle cells with thin processes; large and small foci of red marrow were seen which contained small round cells of deeply staining nuclei. By the trabeculae osteoclasts were found. The same conditions were seen in the parts near the tumour and also in bones remote from them.

The fibrous elastic brown-red tumours were surrounded/

surrounded by fibrous tissue, the cells being chiefly spindle-cells, also round cells. There were many blood spaces; bone trabeculae were seen at the periphery of the sarcomatous structure, where they gradually merged into the fibrous network (in these parts of the tumour are masses of pigment). In other parts of the tumour they were yellowish-red in colour, and here the sarcomatous cells were surrounded by newformed bone trabeculae. Rehn emphasizes the fact that in his case there were no signs of infiltration and no metastases, though the case lasted ten years. Schoenberger and von Recklinghausen's cases lasted $1\frac{1}{2}$ to 5 years respectively. The tumours here and there contained small cysts (the result of previous haemorrhages). Rehn said that in his case transition stages could be seen between the cellular tumour and the new formation of osteoid tissue around it. While there were irregular processes of red marrow, the mass of the tumour was in the fibrous marrow. He concluded that the end product of the giant-celled tumour was the building up of the newly formed but imperfect bone tissue. The tumours were always surrounded by "fasermark" and the bone trabeculae are to be found at the periphery of the sarcomatous structure, where they gradually and imperceptibly go over into the fibrous tissue.

Von Recklinghausen's case (man aged 40).

This was one showing the typical marrow changes of generalised ostitis fibrosa, rarefaction and sponginess of bone and multiple giant-celled sarcoma always embedded in the fibrous marrow; these tumours contained cysts. He considered the tumours and cysts were the first manifestations of the disease, and attributed the distribution of the morbid changes to strain, (i.e., it occurred at the points where the skeleton is more exposed to violence). In explanation of the frequent involvement of the head bones he said this was because they were exposed to the extremes of heat and cold to a greater extent than the rest of the body. In all these three cases multiple fractures were present. Hirschberg, in discussing this view, decided that the osteomalacia was the primary condition, that there was no sign of inflammation in osteomalacia, and that the cyst formation (result of haemorrhage) and the sarcomata (the result of increased cellular activity) were later developments.

Osgoode did a series of metabolism experiments in his case and found an increased calcium excretion with retention of sulphur and magnesium. After castration was performed in his patient, there was marked improvement/

improvement and the calcium excretion became less than normal.

From the above cases it will be seen that no hard and fast line of demarcation can be drawn between osteomalacia and Paget's Disease. In both there is absorption of bone, in the bone this goes on to cyst formation, with increased friability of the bone and consequent multiple fractures, i.e., the osteoclastic activity is the predominating feature.

In the other, Paget's Disease, after the primary absorption, a fibrous kataplasia occurs with proliferation of the osteoblastic cells and formation of osteoid tissue. The bones become thickened and the osteoid tissue, being imperfectly calcified, tend to bend rather than break. In both diseases the condition is a chronic one, and at any time the cells of certain areas may manifest increased activity and proliferate rapidly, becoming less and less differentiated, until they return to the primitive type, i.e., sarcoma. Osteomalacia has been proved to depend in certain cases on some abnormality of internal secretion (e.g., the beneficial result of castration). It may well be suggested that Paget's Disease is merely another phase of a similar process.

From the above it will be seen that there is a striking resemblance between Paget's Disease osteomalacia/

osteomalacia and multiple myelomata, widely though the symptoms of typical cases may differ clinically. In each, one particular type of bone marrow cell is involved in a metaplasia which may go on to sarcomatous development. The differences in symptoms are the result of the particular type of marrow cell involved; if it is an osteogenic cell, deformity of long bones and comparative absence of anaemia are the leading characteristics; on the other hand, if cytogenic cells are involved probably grave anaemia, albumosuria and hence a more rapid cachexia ensue. Myelomatosis, as we have tried to indicate, is not merely a condition of multiple new growths in a normal bone; many observers have already pointed out that these tumours arise in bone that is already the site of retrograde changes. In many cases there is no perceptible tumour until sections are made. Even when the tumours are seen, are they not analogous to the localised ivory masses of compact bone often found in cases of Paget's Disease in the skull or long bones, or to the masses with whorl-like structure and giant cells, referred to in osteomalacia? All three may become sarcomatous. In all there is an absence of metastasis, absence of signs of infiltration and in all some tendency to trophic changes of the skin and to occasional rheumatoid/

OSTEOMALACIA. PAGET'S DIS. OF BONE. MULTIPLE MYELOMATOSIS.

Age.	20-40	50 -70	45 - 65
Sex.	F	M	M
Duration.	Chronic, 2-22 yrs.	Chronic, 1-35 years.	1 - 8 years.
Pain. 1st Symptom	"Rheumatic pains"	"Rheumatic pains."	"Rheumatic pains."
Deformity	Pelvis, Kyphosis, Ribs, Vert. (Some-times Femora). Angular curvature	Long bones, Skull, Clavicles, Vert., Ribs, Broad curvatures.	Ribs, Vert., Sternum, Kyphosis, Skull, (Some-times long bones). Angular curvature.
Fractures.	Very common.	Rare, except when neo-plasms present.	Very common.
Neoplasms- Not sharply de- fined. Not infiltra- tive.	Not sharply de- fined.	+	+
Malignancy	Marked tendency.	+	+
Trophic changes in skin, pigmen- tation, &c.	+	+	+
Arthritis.	+	+	+
Path. Cond's.	Decalcif., & ab- sorp. of bone. Cyst for'n. Osteo- clasts + Fatty & typhoid marrow.	Absorption + imper- fect, new formation of bone. "Fasermark". Osteoblasts, ++	Rarefaction of bone. Proliferation of mye- locytic elements of bone marrow.
Course.	Progressive	Progressive.	Progressive.
Blood Cond'ns.	Normal or mod. anaemia.	Usually normal.	Usually anaemic, but maybe normal.
Urine.	Sometimes albu- mosuria.	Usually normal.	Albumosuria.
	Cachexia. Death	Cachexia. Death	Cachexia. Death.

"rheumatoid arthritis". All occur in middle life; all have an insidious onset with rheumatic pains, a chronic progressive course and a tendency to later cachexia (See chart).

MODE OF ORIGIN OF THESE DIFFUSE NEW GROWTHS.

It is in studying these diffuse multiple new growths that we see the fallacy of Ribbert's and Cohnheim's theories of neoplasia, i.e., that all new growths arise from 'cell rests' and cell inclusions (taking place either in embryonic or later life). In these diffuse conditions the evidence goes entirely to prove that the tumours arise from a metamorphosis of the cells of the tissue in situ and not from any one primary focus. In this connection Landau's case is an excellent illustration of this metaplasia.

Our case is of interest in corroborating this view, and there is little doubt that a study of the borderland zones of the diffuse new growths in other members of this group may prove that they also show similar transition stages.

In all there must be some general abnormality of the cells involved; an instability of the cells, so that in responding to some unknown stimulus they tend to "lose the habit of function and acquire a "habit/

"habit of growth". (Adami.)

The heredity tendency shown in so many members of this group has probably some significance in this connection.

These varied diseases, widely different
as their signs and symptoms are, have many features in common. Particularly to be noted is the frequent hereditary tendency, the tendency to form multiple nodules which merge into the surrounding tissue and the liability of these nodules to exhibit in parts malignant change. Other features they have in common, namely all the new growths may be localized in one region; the individual nodules may follow the same evolutionary course and termination often in sarcoma, and lastly the frequent association of trophic disorders (eczema, pigmentation, arthritis, etc.).

The frequent trophic changes, pigmentation of skin, varicose ulceration, etc. are also characteristic. An interesting fact also is the presence in many cases of chronic arthritis. This seems to be too frequent to be a coincidence and one cannot but be impressed by the probable connection between them.

These diseases are so widespread that the same underlying factor must be a constitutional one.

IX. BLASTOMATOID CONDITIONS:

and their relationship to disturbances of the
INTERNAL SECRETIONS.

These varied diseases, widely different as their signs and symptoms are, have many features in common. Particularly we would go into the frequent hereditary tendency, the tendency to form multiple new growths which merge into the surrounding tissue and the liability of these growths to exhibit in parts malignant change. Other features they have in common, namely all the new growths may be localised in one region; the insidious onset; the chronic progressive course and termination often in cachexia, and lastly the frequent association of 'trophic' disorders (cutaneous pigmentation arthritis &c.).

The frequent trophic changes, pigmentation of skin, varicose ulceration, etc. are also noteworthy. An interesting fact also is the presence in many cases of chronic arthritis. This seems to be too frequent to be a coincidence and one cannot but be impressed by the probable connection between them.

These diseases are so widespread that the cause underlying them must be a constitutional one, due/

due either to some grave lesion of the nervous system or to disturbance of metabolism. The latter, as Lyon pointed out in regard to lipomatosis) is the more probable one, the result of derangement of the glands of internal secretion and a complex correlation of these structures may account for the variety of symptomatology depending on the extent of the morbid process.

GLANDS OF INTERNAL SECRETION: The vital importance of internal secretion has of late years been recognised more and more freely. Howell in a paper on the "Chemistry of body Secretions" states:- "that the complex of activity in the animal body is united into a functional harmony not only through a reflex control exerted by the nervous system but also by means of a chemical regulation effected through the blood or other liquids of the organism. Bayley and Starling have shown that one organ controls the activity of another organ by means of specific chemical substance given off into the blood - hormones.

Starling has also called attention to the fact that some of these hormones act, first, by increasing/

increasing the process of dissimulation, of catabolism; while others apparently stimulate the process of assimilation or growth (e.g. the hormones of the anterior lobe of the pituitary reproductive cells, etc.)

It is not a little remarkable how known disturbances of sundry organs of internal secretion are associated with overgrowth of one or other tissues.

It is easy to understand that any disturbance in this complex correlation of the various glands of internal secretion would lead to widespread results. The pathological changes causing symptoms of disease may be either the result of glandular inadequacy or glandular overactivity. (Adami). It has been proved by many observers, that any pathological change in one of these glands causes disturbance in the functions of the others, e.g. ovarian disease is often associated with pigmentation of the skin which is probably due to disturbance of the chromaffin cells of the adrenals and hypophysis. One gland would also seem able to vicariously take on the function of another should it be diseased, thus disease of the thyroid is associated with hypertrophy of the pituitary body.

MacCallum and Voegtlin have shown that
the/

the parathyroids exercise influence on calcium metabolism, their removal causing deficient calcification of the osseous system.

There is also a curious resemblance between the functions of the various glands. Hyperplasia of the cortical portion of the adrenals is associated in many cases with excessive obesity. Hyperplasia of the anterior part of the pituitary body has been associated with growth activities of the skeletal tissues (Adami).

Ovarian disease is often associated with exophthalmic goitre.

It can therefore be readily understood that any pathological change in any one of these glands, or in several, would cause generalised disturbance of metabolism and the symptoms would vary according to the extent to which the individual glands of internal secretion were respectively involved in the pathological process. Hence it is not surprising that attempts at treatment from extracts of one of these glands alone have had unsatisfactory results in many cases as probably the symptoms were due not to a lesion of that gland alone but also to a varying degree of disturbance of the other members of the group also.

It/

It is impossible not to be impressed with the general parallelism between the early and diffuse blastomatoid lesions and these known results of disorder of the organs of internal secretion.

We feel however that the data at our disposal are as yet wholly inadequate for us to venture to do more than call attention to this parallelism.

(As already pointed out the rare studies that have been made in metabolism in these states support this view.)

At most we would urge that in future Autopsies in Paget's disease of bone and allied conditions particular attention be directed to the ductless glands.

THE/

THE TROPHIC DISEASES OF BONE.

Apart, that is, from the inflammatory and specific granulomata - would therefore seem susceptible to a classification along the following lines - which are here tentatively suggested.

- I. HYPOPLASTIC: A condition of imperfect development of bone.
 - II. ATROPHIC.
 - III. KATAPLASTIC: A condition leading to
 - IV. HYPERPLASTIC: Conditions of primary overgrowth.
-
- I. HYPOPLASTIC:
 - (1) Congenital: Osteogenesis Imperfecta, Achondroplasia, Cretinism.
 - (2) Acquired: Rickets, &c.
 - II. ATROPHIC:
 - Simple atrophy, fragilitas ossia.
 - (Is this not merely a stage of Group III?)
 - III. KATAPLASTIC: /

III. KATAPLASTIC

(A) Osteogenic Elements:

(1) Simple: (a) Atrophy, associated with development of fibrous medulla.

Paget's Disease.

(b) Atrophy, associated with decalcification.

Osteomalacia.

(c) Combination of (a) and (b)

(2) Blastomatoid:

(a) With secondary diffuse and Kataplastic overgrowth of osteoblasts.

(1) Paget's disease with secondary multiple osteoid growths, tending to give rise to malignant sarcomatous developments.

(2) Osteomalacia, ditto, ditto, ditto.

(b) Exostosis and Echondrosis.

(3) Blastomatous: True bone tumours, localised.
 Enchondroma.
 Osteoma,
 Osteo-sarcoma.

(B) Myelogenic Elements:

Blastomatoid - diffuse and Kataplastic overgrowth of Myeloblasts.

i.e. Myelomatosis

(Myeloma - multiple).

IV. HYPERPLASTIC:

(1) Congenital: Developing before puberty - Giantism, Congenital acromegaly.

(2) Developing in later life: Acromegaly, Pulmonary, osteo-orthropathy.

CONCLUSIONS./

XI. CONCLUSIONS.

1. The main histological features of Paget's disease are, a progressive reduction of certain of the bones, together with a characteristic replacement of the ordinary by delicate fibrous or fibrillar marrow.

Associated with this there is a striking disappearance of the lymphoid and myeloblastic elements in that marrow.

2. This presents no indication of being an inflammatory process, or an after result of the same but has all the marks of being an atrophic process, coupled with a certain grade of kataplasia or modified conditions of the function of the osteoblastic elements.

In a certain percentage of cases of Paget's disease, this process is complicated by a further modification of the osteoblastic elements in different regions of the bone, characterised by a more active proliferation of the osteoblasts in these regions and replacement of the simple fibrous by a fibro-hyaline matrix.

3./

3. Where this condition shows itself, the overgrowth is diffuse, involving progressively the osteoblasts over larger and larger areas, leading thus to an osteoid overgrowth.

4. Careful study of the features of this overgrowth indicate that here we deal with a blastomatoid condition and not with the development of true localised tumours of the ordinary type, or blastomas proper.

5. Such blastomatoid outgrowths may give origin in certain portions of the same, to definite malignant sarcomatous development. Whereas the simple blastomatoid growth is purely local and respects the original boundaries of the tissue, having no tendency to infiltrate, regions of the sarcomatous growth do not respect these boundaries and infiltrate the surrounding tissues.

6. A survey of neoplastic states in general shows that this blastomatoid growth, as distinct from unicentric (or pluricentric) sharply defined centrifugal tumours of the ordinary type - is more frequent than is generally recognised.

Examples are given of such blastomatoid conditions involving fatty tissues, neural tissue, neuroglia/

neuroglia, lymphoid tissue. It is shown that members of this group have many features in common, e.g., hereditary tendency, tending to multiplicity of growths, merging into the surrounding tissue, the presence of trophic changes elsewhere, and tendency to late sarcomatous change.

Next the subject of the Leukaemias and pseudo-leukaemia and chloroma is touched upon and extracts given from eminent authorities showing the growing tendency to recognise their probable relationship on the one hand to neoplasia and on the other hand to diseases of bone marrow.

7. In connection with bone. - Multiple exostoses are characteristically diffuse, localised overgrowths of perfectly formed bone, not sharply separated off from the surrounding bony matrix, and these must be regarded as blastomatoid types.

8. But in addition to such primary blastomatoid, and the secondary blastomatoid states, as already noted, occurring in Paget's disease, the myeloblastic elements of the bone may exhibit a similar diffuse growth.

The so-called Myeloma multiplex can only be regarded as a myelomatosis or blastomatoid overgrowth/

These considerations, coupled with the fact that metabolism experiments in Paget's disease, osteomalacia and the allied conditions, indicate grave metabolic disturbances, suggest that in future more exact studies be made upon the condition of the ductless glands in Paget's disease and the associated conditions. The data at present in our possession are too inadequate to permit us to lay down with any precision, that these tumours are primarily due to some disturbed equilibrium between the various internal secretions. But studying and analysing the very numerous hypotheses that have been advanced in connection with Paget's disease, it may be said that the hypothesis of some constitutional disturbance of metabolism has more in its favour and less against it than any of its fellows.

11. A tentative classification is afforded of what may be termed the "trophic bone disturbances" and the thesis closes with an analysis of cases upon which the paper is based, together with a table recording all cases of Paget's disease in which the diagnosis has been well established by autopsy, X-rays or microscopic examination.

A full classified bibliography of recorded cases of Paget's disease of Bone, and other works consulted is also appended.

ANALYSIS of 170 CASES of PAGET'S DISEASE of BONE.

AGE, between 50-70	55.9%	Localised Paget's Disease	11.2%
Youngest case 17, oldest 93.			
SEX: 60% = males		Skull involved	87.6%
DURATION: 55% = 5-20 years.		Nervous Symptoms or Disease	9.4%
ACCIDENT, before onset: -	11.2%	Eye Symptoms	4.7%
ILLNESS, before onset	4.7%	Deafness	8.2%
HEREDITARY Paget's Disease	7.6%	Cardiovascular	31.1%
" Cancer	4.1%	Varicose Veins & Ulcers	1.9%
" Nervous Disease	12.4%	Congenital Syphilis 3 certain 2(?)	
PAIN	57%	Acquired "	2.9%
GENERAL DEFORMITY	60%	Wassermann Reactions 8=all negative.	
		Arthritis	7.1%

CASES of PAGET'S DISEASE of BONE with NEOPLASIA.

NEOPLASMS	A. <u>Benign</u>	(1. of bone 2 certain, - 2 doubtful
" 29 certain.	13 certain.	(
" 8 doubtful.	5 Doubtful.	(2. of other tissues, 11 certain, -3 ?
	B. <u>Malignant.</u>	(Sarcoma (Bone, 10 certain, 3 doubtful
	16 certain	(Other tissues, 2 certain.
	3 doubtful.	(Cancer (Bone
		(Other tissues = 4

DEATHS 38

AUTOPSIES:- with neoplasm = 17
without " = 14

Blood Examinations 15. 11= normal
3= mod. anaemia
1= eosinophilia.

Other diseases associated with Paget's Disease:- Huntington's Chorea;
Bulber Paralysis; Dupytren's Bright's Disease;
Elephantiasis; Raynaud's Disease; 4 Goitres.

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RECORDED CASES OF PAGET'S DISEASE OF BONE.

HISTORY OF PATIENT.				SIGNS AND		SYMPTOMS.							Spontan- eous Frac- tures.	Results.	Operation or Autopsy.	Remarks.
No.	Author & Reference	Age	Sex	Duration of Illness	Previous Illness or Accident.	Family history.	Pain	Deformity.	Nervous Sys- tem & special senses.	Cardio- vascular System.	Syphilis	Necplasms.				
1	Sir James Paget: Med.- Chi. Trans., Vol. LX, 1877, p. 37.	69	M	22 years.	Gen'l health good till a few months before death.	1 sister died cancer of breast. No gout.	Aching pain in legs, 6 mos. before death. "Neu- ralgic" pains in left arm.	Lt. tibia + broad surface nodular, base elongated. Femora ++ Pelvis + Head ++ 27½" Kyphosus lost 4" hgt. Chest contr. Simian attitude.	Retinal haem- orrhages. Deafness.	Arterio- sclerosis + Cardiac hy- pertrophy.	Iodide treat- ment did harm.	Tumour upper 3rd radius: metastases in skull bones, pleurae & med- iastinum. Micr: Spindle- celled sarcoma.		Death from cachexia.	Tumour:- Upper 3rd lt. radius, large ovoid mass of pale grey & white cancerous sub., similar to nodules in pleurae & medias., but with growths of bone extending into it. Skull:- Some malign., nodules embedded in bones of skull. Periosteum:- Normal thick- ness, whole surface finely porous & finely reticulate. Inner surface smooth & little changed except deepening of all the grooves for b.v.s. The cross-sect.: -cavernous bone spaces filled c soft reddish substance. Long bones:- Periost., not visibly changed, outer surface irreg., & finely nodular, deeply grooved for b.v.s., whole structure of bone changed to porous coral-like sub. Micro:- H.S. dim'd; H.C.s widened irreg'ly & cont'g irreg. staining homogeneous subs. cont'g cells of different kinds are leucocytes also fibro-cells & myeloid cells; b.v.s not unduly large. Walls of some canals contain osteoblasts.	In 1870, acute & fluid inflam'n of right knee which gradually subsided. General health good till 3 mos. before death, then rapid emaciation and cachexia.
2	Paget. Med.-Chi. Trans. Vol. LX 1877, p. 48. Also Anman- dale.	55	M	Many years.	General health good.		Severe in limbs.	Curv. & thick'g of legs & thighs. Rt. humerus. Kypho- sus.				Large tumour of upper part humerus very vascular, "med- ullary cancer" giant-celled sarcoma.	Right hum- erus.	Death after operation.	Operation: Amputation at shoulder- joint. No p.m.	General health unim- paired.
3	Howse. B.M.J. 1878, Vol. I, p. 69.	65	F	2 years.			Severe in right leg.	Tibia thicken- ed & curved.				Soft mass in- ner side of head of tibia.		Death from metastasis.	No autopsy. Exam. of oper'n specimen:- Tumour of tibia large spindle-celled sarcoma. Sections of tibia (remote from tumour) seen by Paget & pronounced typi- cal of Paget's disease.	Author refers to probable connection between Paget's Disease and tumour forma- tion.
4	Lunn. St. Thomas Hosp. Report, Vol. XIII, 1883, p. 44.	70	M		No gout. Gen'l health good, till present illness.		Severe in limbs.	Skull ++ Clavicle + Rt. humerus + Kyphosus ++ Femora + Tibiae ++		Slight		Large chondro- ma of ileum; acetabulum friable and nearly destroy- ed by neoplasm Fem. & inguin. glands swollen. Fem. vein adh. not so ossified		Death from cachexia.	Autopsy: Skull thickened and leg bones porous. Sections show irreg. structure of bone. Absorption: the predominant process producing large & irreg. Haversian canals, also evidence of a formative ostitis.	Author thinks the appearances are not those of inflammation.

RECORDED CASES OF PAGET'S DISEASE OF BONE.

HISTORY OF PATIENT.				SYMPTOMS		AND	SIGNS.						Results.	Operation or Autopsy	Remarks.	
No.	Author & Reference	Age	Sex	Duration of Illness	Previous Illness or Accident.	Family History.	Pain	Deformity	Nervous System & special senses	Cardio-vascular system.	Syphilis	Neoplasms.				Spontaneous Fractures.
5	Goodhart, B.M.J.1878, p.69.	60	F	6 months.			In back and legs	Skull much thickened; iliac crests++ long bones not affected.	Paraplegia from pressure of tumour			Large sarcoma in each iliac crest, also in lower dorsal vert., & 2 in skull. No micro. descr'n of tumour		Death.	Osteoarthritic changes about many vertebrae. Skull 4/5 in. thick, bone heavy but porous; two small sarcomata in it also. Long bones not affected. Pyelitis.	Rapid emaciation and cachexia. Very short report of case. Dr. Goodhart suggests that Paget's disease might be a gener'ed form of tumor of bones.
6	Goodhart, Ibid.	55	M.	6 months.	Gonorrhoea. Gen'l health good.		Severe.	Skull thick'ed Ilium dense & heavy.				Periosteal sarc. of ilium, femur, clavicle, med. glands & both suprarenals.		Death.	Skull thick, porous, -diploe gone. No microscopic description.	No tumours appeared till a late stage of illness, then rapid emaciation ensued.
7	Pitts & Shattuck. Trans. Path. Soc., 1897, p.184. MacKellar's case.	58	M	20 years.	General health good		Aching pain at night.	Rt. Femor.-Tib. & Fib.++for 20 yrs; lt.leg also++6 mths. Scap. hip-bone & spine+				3 small tumors on head of tibia.		Operation, in statu quo.	Lt. leg amputated. Path.report on leg:- Whole tib.enlarged; in head & adjoining part tumor about 5" vert. diam. New growth undergone cystic degen. Micro:- Highly cellular neoplasm of spindle-cells & giant-cells, in some areas fibrous metaplasia, -in portions the texture more open, -branching cells with mucous or oedematous spaces.	Lt.leg & knee greatly swollen during rapid growth of tumors. Reported:-Patient convalescent after operation.
8	Packard & Steele. Amer.Journ. Med. Science Nov.1901.	62	M.		Patient deaf & knew no English, ∴ no history.			Head ++ Tumor of left frontal bone. Clavicles + Humeri + Bones of rt. forearm + Kyphosis Pelvis + Femora ++ Tibiae ++	Deaf. Mental weakness.			(1) Soft tumor of lt.front.bone 4x5 cm.=base 2 cm.elev'n, = sarcomae. (2) Diaphragm =typical giant-celled sarcoma, (no slides of tumour)		Death.	Calvarium thick'd (1½-2cm).Diploe appeared absent except in frontal region. Tumour, brain adherent to tumour; small white tumor nodules over 3rd frontal convol'n, also in lt.pleura. Bones: Microsc:- (1) Absorpt'n of healthy bone. (2) Form'n of new bone coincident, but in no way connected with absorption process. (3) Failure of calcification in this new bone. (4) Destruction of regular structure of the bone & addition of new uncalcified bony tissue (5) Formation of fiant-celled sarcoma in the affected portion of the skull. Thyroid nod examined. Spleen 13x8x3.5 cm. Hypophysis=normal. Suprarenals microsc.normal. Long bones:-finely porous structure in which areas of unaffected bone alternate with spaces which are result of its absorption. Spaces = filled with fibrous tissue reticulum, cells chiefly spindle, also many round cells, & a few Polym. & R.B.C & fat cells, spaces & vascular giant c lls near the edges of the unaffected bone. Running through these interspaces and through the bone itself are masses of finely	No Remarks. P.M. Continued. packed cells, osteoblasts with a fibrous matrix. Skull with but few giant cells.

RECORDED CASES OF PAGET'S DISEASE OF BONE.

HISTORY OF PATIENT				SYMPTOMS AND		SIGNS.		Nervous Sys-tem & special senses.	Cardio-vascu'r System.	Syphi-lis.	Neoplasms	Sponta-neous Fractures.	Results.	Operation or Autopsy.	Remarks.
No.	Author & Reference	Age	Sex	Duration of Illness	Previous Illness or Accident.	Family History	Pain.	Deformity.							
9	Fielder. Lancet 1896, Vol.I,p.1428.	42 yr.	F.	6 years.		Husband syphilis.	Severe in legs.	Bowing of legs 4" lost in hgt. falling in of ribs,most of long bones affected except feet, radii & ulnae.			Sarcoma of sacro-iliac joint.		Death.	Cranium 1½" thick in parts. Vertebrae ankylosed together. Tumour mixed, round and spindle-celled sarcoma.	Specimens shown at Med. Society meeting. Very short report on case.
10	Rehu. Vertrand et Deutsch. Geselt.f.chir P.104.P 424.	23	F	9 years.	Always over-worked & under-fed.		Severe in affected limbs.	Scoliosis. Tibiae + Femurs +			Tumor-Rt.ulna,round-celled sarcoma op. Rt.femur round celled sarcoma op. Rt.tibia,8th & 9th ribs,lt.pelvic brim lt.tibia,8th rib, spindle & round-celled sarcoma. Rt.Fibula.	Right & left Femora	Death from cardiac weakness.Bones apart from tumours showed typical Paget's change.	Two kinds of tumours:-some dark red round-celled sarcoma; some with yellow spots = spindle-celled with new form'n of bone; no definite margin but gradual transition. Other organs not described.	X-rays showed typical Paget's bone & multiple tumours.Temp.normal. No albumosuria. Cardiac weakened. Consistence of tumours varied.On sec- some dark red,some pale In ad.to tumours,bones showed marked changes.
11	Cayley. Trans.Path. Soc.1888, XXIX,p.172.	65	M	4½				Skull + Lower jaw + Left clav+ & deformed. Tibiae ++			Medullary cancer of right lung.Nodules on rt. pleura,Bronchial glands & in liver.		Death	Medullary cancer of diseased bones increased in size irregularly and occupied by cancellous bone with wide meshes containing a gelatinous material of yellowish colour.	No malignant foci found in bones.
12	Goodhart. B.M.J.1888, Vol.L,p.644.	65	M	15				Head + C ₂ 25½" Femur curved & thickened.Tib-iae " " Kyphosus + Clavicles +			Lymphomata in Spleen.Malignant nodules in liver & pleura;also malig. glands in media-stinum & abdomen.		Death.	Skull heavy & soft,13/4" thick. Clavs.++ Long bones more curved than thickened. Section = Spleen++ full of large circumscribed yellow masses=lymphomata.	Good general health till 4 months before death. Then great emaciation.
13	Wightmain Arch of Med. 1883,Vol.X, p.146.	20	M	3 years.		Good	Pain in legs,hips & back	Femora + Tibia+waddling gait.Pelvis+ Vert.bodies+ & spongy. Spongy enlarg. of knee-joint.			Tumours of liver & spleen. Cancer of the omentum. Encephaloid.	Some years before fell 30 ft. No bones broken,but few weeks later pains in legs. Rheu-matic?	Death.	Peritoneum entirely filled with tumour= encephaloid cancer of omentum. No note of microscopic examination of the bones.	Swelling of knee, no fever. Antirheumatic treat.& Pot.iod.no good Cancer began 4 months death. Bowing of legs, deformed pelvis. Spinal cord not examined.

RECORDED CASES OF PAGET'S DISEASE OF BONE.

HISTORY OF PATIENT				SYMPTOMS AND		SIGNS.		Nervous System & special senses.	Cardio-vascular system.	Syphilis.	Neoplasms	Spontaneous Fractures.	Results.	Operation or Autopsy.	Remarks.
No.	Author & Reference	Age	Sex	Duration of Illness	Previous Illness or Accident.	Family History	Pain								
14	Moizard & Bourges. Archiv. de Med. exper. 1892, p. 479	73	M	50 yrs. since 1st. symptom.							Circular epithelioma of pylorus.	Fracture (no fracture or wound) Illness dates from this contusion of lt. leg. 4 yrs. before case reported, fracture of rt. leg. Hyper. of tibia.	Death	Microscopic exam. of bones:- rarefaction and condensation of bone; vessels irreg., lymphocytes & giant cells; large granular protoplasmic masses which stain badly; nuclei stain poorly, became yellowish with picrocarmine. No evidence of sarcoma of bone.	One frequently finds the coexistence of visceral cancer with osteitis. Femur:- In the Hav. canals are massed cellular lymphatic elements & protoplasmic masses. 18 mos. before death devel. of cancer of stomach.
15	Koch. Versamm. der Deutsch. Pathol. Gesell. 1909, p. 107.	65	F	20 years	Always healthy	Father insane	Headache.	Symmetrical thickening of skull. Molar base also + Kyphosis. No abnormality of long bones	ringing in the ears, sl. deafness	Hyper. of heart. Arterio-sclerosis.	Wassermann negative.	Rt. breast:- tumour size of child's head, brown & oedem. Poor in cells, coarse fibrous structure, studded c glandular remains & cysts, also a few islets of cartilage. Adenoma of kidney	Death.	Hypertrophy of heart, no valvular lesion. Spleen 12:6½:3cm., firm and on section-lymph nodes distinct. Thyroid normal. Adenoma of kidney. Skull 30-60 m.m. thick. Grooves for vessels deepened. Empyema of right frontal sinus. Micro:- Dif. between inner & outer tables of skull & diploe lost. Irreg. network of irreg. staining bone trab. Against the bony tract one finds rows of osteoblasts which lie in an osteoid matrix. Here & there in Howship's lacunae lie myeloplaxes. Here & there in skull are dense calcium concretions.	Pat. said her head was quite small before onset of P.I. report hyperostosis of aud. canal. Blood pressure with Rocci = 210. Intelligence normal.
16	Robinson. Trans. Path. Soc. Vol. 38, p. 262.	52	M	11 yrs.	Pat. says his brother died of illness like his own case, 2 of Pat.'s children died aet. 7 & 8 yrs, with enlargement of skull	Brother an imbecile. One brother died some yrs. prev. & deform. of legs.	Pain & weakness in back	Lt. tibia thickened & bowed. Head + 24½". Lt. Femur + Clav. + Left tibia + Rt. tibia + Lt. femur + Rt. femur + Humeri + Kyphosis dorsal.	Intelligent, but irritable. No symptoms. Dull headache. No alteration in vision; no paralysis of ocular muscles. F. oculi normal.			Round-celled sarcoma of rt. hemisphere of cerebellum, size of tangerine orange.	Death.	Skull, rt. side (unilateral) thickening, & spec. on occipital and parietal regions. Save at its thickest part no diploe left. 1 section looks like (Plaster of P.) bone rarefied. Greater portion of outer surface riddled with foramina. Inner surface grooved deeply for vessels.	On adm. to Hospital- pulsating area in region of post fontanelle. Sarcoma cerebelli. Hereditary case.
17	Ravenna. Nouv. Icon. del. salp. 1909, p. 524.	58	M	15 yrs.	M + = Ovarian cyst S. + cancer.			Left leg + curved. Head + + Clav. + + Arm bones + + Femora + + curved		Arterio-sclerosis	Wassermann neg.	Gastric cancer. No free tumour.	Patient left Hospital very ill.		Emphysema. Muscular atrophy of legs. Gastritis some months, weakness & emaciation. Ulcer on right leg. Blood = moderate anaemia.

RECORDED CASES OF PAGET'S DISEASE OF BONE.

HISTORY OF PATIENT							SYMPTOMS AND		SIGNS.					Results.	Operation or Autopsy.	Remarks.
No.	Author & Reference.	Age.	Sex.	Duration of Illness	Previous Illness or Accident.	Family History.	Pain.	Deformity.	Nervous System & special senses.	Cardio-vascular System.	Syphilis.	Neoplasms.	Spontaneous Fractures.			
18	Cohn. Berlin Klin. Wocheusch 1907, p.755.	64	F	For 20 yr		Good		Grad.increase in size of skull which is greatly thck'd all over vault Surface smooth all over.	n.a.d. Deafness Eyes.	Arterio-sclerosis.		Lipoma of right breast.		In statu quo.		Shown at Med. Soc. meeting; agreed it was probably Paget's Dis. confined to the skull. All agreed it certainly not leontiasis ossea.
19	Stelling. Virchow's Archives, Vol.CXIX, p.547.	70	F	8 yrs.	Mental instability.		Rheumatic.	Head for 3 yrs left arm & legs Swellings in region of 1 st font., another in temp.reg'n, 3rd rt.parietal eminence.	Mental weakness senile dementia			Small glioma of spinal cord central region.		Death.	Head large size .Circ.61.5 cm.H'gt 20.5. Breadth 17.1.In region of rt. eyebrow 15 mm.x 6 x3 cavernose swelling. Ependyma granular.Lat.ventr.enlarged.Chor. plex small cysts. Spleen 170 gr.Many small chalky nodules.	Outer surface of skull uneven. The swellings on the skull are red & porous.Small tumor behind central canal of spinal cord at level of 5-6 ribs.Small glioma.Otherwise nothing abnormal in C.N.S.
20.	Stelling. Virchow's Archives, Vol.CXX, p.563.	92.	F.		No history obtainable		Left leg, esp.tibia.		Nerves microscopically normal.	Arterio-sclerosis.		Subserous myoma uteri.		Pat. died on adm.to Hosp.		Microscopical appear in the bone sections typical.
21	McPhedran Med.News, Phila.1885, p.617.	63	F	6 years			In right leg.	Rt.tibia + & then Femur.Lt.T. & F.slightly + standing with heels together, the knees are 2" apart.	Right Hemiplegia at 57. Some months later P.I.			Malignant disease Tumour (nature unknown) below liver & free from it.		In statu quo.		Healthy till aet.45. P.I.dates from rt.hemiplegia 7yrs. before. Tumour hard,smooth, painless,size of large orange,Gen'l H. fair. No note as to possible etiology of tumour.
22	Gibney. Med.Record N.V.1890, Vol.I,p.453	50	M	5 years		Good	Pain on handling limbs.	Knees 6" apart on standing c heels together Head++ Arms+ Internal condyles of humeri +				Over each thigh in the upper & outer aspect is a mass wh.seems like a fibrous tumour, it is connected apparently with the Tensor fascia Femora.		In statu quo.		Disease began without ¹² any inflammatory sign & unprecedented by any acute illness. General health good till P.I. Now getting weaker. Fibrous tumours (?)

RECORDED CASES OF PAGET'S DISEASE OF BONE.

HISTORY OF PATIENT				SYMPTOMS AND		SIGNS.								Results.	Operation or Autopsy.	Remarks.
No.	Author & Reference.	Age.	Sex.	Dura- tion of Illness	Previous Illness or Accident.	Family History	Pain.	Deformity.	Nervous System & special senses.	Cardio- vascular System.	Syph- ilis.	Necplasms.	Sponta- neous Fractures.			
23	Willard & Andrus. Univ. of Penn. Med. Bul. 1904-05, p. 256.	53	F	5 years.		Good	Dull ach- ing pain in thigh.	Rt. leg, gradual bowing of femur Kyphosis espec. in cervical re- gion. Rt. leg 2" shorter than left, thickened & curved. Right tibia + Lt. t. + Thorax deformed. Head, circ. 23" + Claws + Arms normal.		Arterio- sclerosis Mitral disease.		Cystoma of ovary.	5 years ago, as result of violent injury, fracture of left femur. Good union.	In statu quo		Thyroid not enlarged. Mitral disease, oedema of left. Cystoma of left ovary. Treat. c digitalis cleared up the visceral symptoms but proved the Paget's Dis. with progress.
24	Bartlett. Yale Med. Jour. 1910, p. 367.	53	F	Not strong for 6 yrs			Headaches	Past 1½ yrs. = head grad. in- creasing in size. No changes visible in long bones with naked eye.	Some epileptic fits in early adult life. Head- aches.	Arterio- sclerosis.		Submucous myoma uteri.	Fell on head 7 years be- fore.	Death.	Broncho pneumonia + Diffuse hypertrophy and rarefaction of skull, enlarged pituitary gland. Skull = very soft, almost cancellous bone and red in colour. B. vs. at base of brain showed no thickening. Femur: - marrow red, compact bone of shaft: - more vascular than usual & the H. canals: - enlarged indicating a beginning absorption of bone.	Gen'l health good till P. I. Grad. Blood normal. Mitral ste- nosis. Thyroid not en- larged. Micro. of Skull under periosteum hard- ly a trace of compact bone. Pituitary ant. lobe showed striking prepond. of large poly- gon cells over the small cuboid cells.
25	Saunders. West London Med. Journal, Vol. II, 1906, p. 27.	69	F	Many years.	Good		In back & head.	Head + also mal- ar bones + Zygoma Spine = Kyphosis Femora, tibiae + 1 curved. Fibu- lae, bones of arms	Acute iritis. Slight deafness					In statu quo.		Slight goitre for 30 years. General health unaffected.
26	Herwisch. Codex Med. Phila. 1895-6 p. 203.	71	F				Rheumatism at onset of P. I.	Head + circ. 27". Femora + Left tibia + + Right tibia + Ribs & pelvic bones +	Irritability; Insomnia. Intellect dull.		+ +	Exostosis of lower end of femur.		Death.	+ Skull soft & thick = 1 3/8" in diam. Diploe almost absent. Brain healthy. Pituitary heal- thy. Femora thickened & curved. Epiphysis much enlarged & covered with a new growth = exos- tosis of similar friable mealy bone. Atheroma. Hypertrophied heart, Suprarenal & thyroid not mentioned. Emphysema. Microscop: - Femur absence of bone cells & irreg. enlarged Hav. Systems. Lt. Tibia: - atrophy of bone, loss in number of osteophytes & osteo- blasts, conversion of part of bone into mere fibrous tissue, the marrow contains very few	<u>No Remarks.</u> <u>P.M. Continued.</u> myelocytes. Bone decalcified in 1/6 of usual time.

RECORDED CASES OF PAGET'S DISEASE OF BONE.

HISTORY OF PATIENT.				SYMPTOMS AND			SIGNS.										Results.	Operation or Autopsy.	Remarks.
No.	Author & Reference.	Age.	Sex.	Duration of Illness	Previous Illness of Accident.	Family History.	Pain.	Deformity.	Nervous System & special senses.	Cardio-vascular System.	Syph-ilis.	Neoplasms	Spontaneous Fractures.						
27	Helléreau. These de Paris, 1901.	63	F	13 years	Gen'l health excellent till aet 50.	Good.	Pains in legs.	Rt. leg + curved, lt. leg ++. Arms & forearms + Clavicles + Head slightly + Kyphosis.				Swelling size of pigeon's egg above lt. malar bone. On lt. clav. swelling size of tangerine orange.		In statu quo.		Very short report.			
28	Sommer. Amer. Med. 1903 p. 229.	63	M.	18 yrs.		Good.	Rt. leg & thigh	Stooping shoulders & bowing of legs. Head + lost 12" in hg't. Clav. ++ Humeri ++	Melancholy. Insomnia. Knee jerks Deafness Pupils unequal, no r'n to light.	Arterio-sclerosis.	+	Were these "growths" not neoplasms?	Fracture of rt. Femur 5 yrs. after onset.	Death.		Thyroid not palpable. Hyperostosis of condyle of humerus. OEdema of lt. leg & redness & swelling for some days. Vault of hard palate encroached by "bony growths." Last 3 yrs. great emaciation & weakness. Temp. 99-103 before death for 6 wks. Marked oed. & red after this had somewhat subsided the hyperostosis at lower end of thigh seems increased.			
29	Negellan. These de Paris, 1903.	71	F				No pain	Clavicles ++ Head + Femora ++ Tibiae —						In statu quo.		Elephantiasis of right leg.			

CASES SHOWING SIGNS OF BOTH OSTEOMALACIA AND PAGET'S DISEASE OF BONE.

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